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Late Cortical Cerebellar Atrophy

A Form of Hereditary Cerebellar Ataxia

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INTRODUCTION

WITHIN the large and confusing group of disorders known as cerebellar atrophies, the variety commonly called parenchymatous cortical cerebellar atrophy has gradually emerged as a recognizable, reasonably uniform, and perhaps specific clinical-pathological entity. Many of the reported cases, including all of the earlier ones, appeared as isolated instances without "familial" or hereditary history. For this reason, primarily, there has been a widespread tendency to regard the cerebellar degeneration as secondary to extrinsic factors of great diversity. Marie, Foix and Alajouanine (1922) who were the first to classify the condition clearly, laid great stress on antecedent infection (scarlet fever and typhoid fever) as the probable inciting cause and called upon the somewhat nebulous notion of "abiotrophy" to explain the late onset and slowly progressive course of the cerebellar disorder. Struck by the similarity of the selective damage to Purkinje cells in parenchymatous cortical cerebellar atrophy and in the encephalitis induced by the virus of louping-ill, Parker and Kernohan (1933) suggested that previous virus infection might be responsible for some cases. Other authors have implied a more direct infectious or toxi-infectious etiology. Thus Rossi (1907) was inclined to implicate a diarrhoea that was present in his patient just before the onset of cerebellar symptoms, and spoke of "auto-intoxication." In the case of Guillain, Garcin and Bertrand (1931), the cerebellar degeneration was complicated by the presence of two small tubercles in the cerebellum and these writers attributed the otherwise typical cortical cerebellar atrophy to slow toxic action from tubercle bacilli. Other writers, among them Kirschbaum and Eichholz (1932) and Stender and Lüthy (1931), have been impressed by the association with alcoholism in their cases and regard this intoxication as significant etiologically. As might be expected in a disease when the onset is ordinarily in the fourth to sixth decade, cerebral arterio- and arteriolar-sclerosis is frequently observed pathologically. This led Archambault (1918) to attribute the cerebellar changes

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in his case to deficient nutrition from narrowing of the pial arteries, although no truly ischaemic changes in the cerebellar cortex were described by him. More recently Courville and Friedman (1940) have offered a modified circulatory explanation which would make the close approximation of the tentorium to the superior surface of the cerebellum a cause for deficient circulation in that area.

As the writer has pointed out in a previous publication (Richter, 1940), none of the proposals to explain parenchymatous cortical cerebellar atrophy as an acquired condition has been convincing. The very multiplicity of the supposed direct or predisposing causes makes one doubtful of their validity. Furthermore, most of the factors mentioned are of very common occurrence, while this type of cerebellar atrophy must be considered rare, although probably much more common than has been supposed. On the other hand, there are now several well studied cases on record in which familial or hereditary incidence cannot be disputed. These will be discussed in more detail later. This report deals with a study of three patients, with autopsy in one, from a family in which fifteen cases of the disease appeared through three consecutive generations. The data appear to show clearly that parenchymatous cortical cerebellar atrophy is in fact a primary heredo-familial degeneration.

CLINICAL AND PATHOLOGICAL DESCRIPTIONS

Case 1. J. S., a widow 86 years old, now a bed-ridden chronic invalid, had always been well and strong until about age 70 when instability of gait appeared insidiously and slowly progressed until it became quite impossible for her to stand or walk. Within a year or two after her equilibrium became impaired she began to drop objects from her hands and became more and more awkward and inaccurate in the use of her upper extremities. Still later, her speech was affected; enunciation became slurred and her voice high pitched. She retained good vision and hearing and her mental faculties were thought by her family to be unusually well preserved until the past year when her memory failed rapidly and she became somewhat childish.

She was admitted to the Albert Merritt Billings Hospital October 30, 1943. Her appearance was that of a thin, shriveled, senescent woman. There was evidence of advanced generalized arteriosclerosis with associated hypertension (200/95), but there were no other significant general physical findings. Superficially she seemed bright and alert and was often found reading a newspaper but it was soon apparent that there was great impairment of her mentality. She could not remember the date of her birth or that of her son or his age, nor did she remember much of what she had just been reading. She knew where she was, but on Thursday, December 9, 1943 she said the day was Tuesday, August, 1942. She confabulated a great deal and smiled in a fatuous, childish way at almost everything.

There were a number of outspoken neurological signs, chiefly cerebellar. She was unable to stand or walk, partly owing to complete inability to keep her balance and partly because of flexor postural changes at the knees and ankles. There was a striking inability to execute voluntary conjugate eye movements in any direction or to converge. At best only a brief deviation of about 5° was possible. Automatic reactive movements of the eyes were performed much better and when she did so there was a rather course, slow, sustained nystagmus with the rapid component in the direction of gaze. No actual strabismus was present. Her voice was thin and piping and her speech extremely dysarthric, often unintelligible, with

slurring of consonants and, at times, a sing-song cadence or even explosiveness. There was no evidence that bulbar or pseudobulbar weakness was responsible for the speech disturbance: there was no dysphagia; palatal movements, both voluntary and reflex, were of good amplitude, as were movements of the tongue, and there was no increase of the jaw-jerk.

Other than generalized senile wasting of the extremities there was nowhere any true localized atrophy of muscles and no fibrillations. Strength was as great as might be expected in all movements of the arms and legs. There was gross asynergy with wide oscillations and dysmetria in both arms, not only in the finger to nose test, but even when the hands were lifted from the bed or used to hold a newspaper. This incoordination was of such a degree that it prevented the patient from feeding herself. Plastic, coarsely jerky hypertonus in passive movements at the elbows was regularly present. Similar but less marked rigidity was found at the shoulders, none at the wrists. All tendon reflexes in the arms were generally diminished. Resting tremor was never observed in the arms or hands.

Both lower extremities were held usually in strong flexion at hip and knee and there were flexor contractures of the hamstring muscles such that the knees could not be extended to more than 170°. The left foot was held in a position of sharp dorsiflexion to an angle of about 20° and could not be passively plantar-flexed to more than 45° owing to contractures. The toes of this foot were in an extreme "hammer" position, hyper-extended at the metatarsal joints and strongly flexed at the phalangeal joints. There was a less marked but similar posture at the right ankle. In the legs there was no muscular rigidity. On the contrary, obvious hypotonia was present, especially of the quadriceps groups. Extreme ataxia accompanied all voluntary movements of the lower extremities and was equal on the two sides. This showed itself by gross wavering, oscillation, and dysmetria whenever the feet were lifted from the bed as well as in the heel-to-knee test which was grossly inaccurate. Most of the time there was a slow, coarse tremor at the left ankle when the leg and foot were in complete repose on the bed. Usually the tremor took the form of an alternating eversion-inversion movement, but sometimes changes its pattern to flexion-extension. The rate was 3-4 per second. From time to time it subsided completely for brief periods. Both patellar reflexes gave minimal responses. The Achilles tendon reflexes were not obtained. The plantar reflexes appeared to be flexor, so far as they could be judged in the presence of the postural deformity of the feet. There was no significant sensory loss. Position sense in the hands and feet was good, vibratory sense fair.

Routine blood and urinalyses were normal, as was the blood Kahn reaction. Roentgenograms of the skull were normal. Attempts to obtain spinal fluid were unsuccessful because of advanced senile osteo-arthropathy of the spine.

The patient died of broncho-pneumonia on July 26, 1944 after a clinical course of some 16 years.

Pathology of the Central Nervous System

Gross: The leptomeninges were notable only for abnormally large amounts of melanin pigment over the orbital surfaces of the frontal lobes, the inferomedial parts of the temporal lobes, the pons and medulla. Advanced atheromatous changes were present in the arteries of the circle of Willis and there was a saccular arteriosclerotic aneurysm of the right internal carotid artery at the point of origin of the middle cerebral branch. It was 0.6 x 0.8 cm. in the diameter and its walls were paper-thin but intact. There was a moderate degree of generalized convolutional atrophy, somewhat greater in the superior frontal and central regions than elsewhere. More striking than this was the small size of the cerebellum. The cerebellar atrophy appeared to be generalized and proportionate throughout the organ. There was little, if any, reduction in size of the pons and the medulla and olives were normally promi-

nent. The entire brain, after hardening in formalin weighed 1065 g., the cerebellum and brain-stem 115 g. Thus the cerebellar atrophy, while obvious, was moderate (fig. 1).

In coronal sections through the cerebral hemispheres the most noteworthy changes were in the lenticular nuclei. These were somewhat atrophic, discolored light brown, and the markings were indistinct, including those separating the pallidum from the putamen. Throughout the lenticular and caudate nuclei there were numerous minute lacunae around the thickened and prominent blood vessels giving these structures a somewhat porous appearance. A similar cribriform state existed in the convolutional and deep white matter of the frontal lobes and in the dentate nuclei. There were no gross changes in serial transverse sections through the brain stem. The substantia nigra was well developed and normally pigmented.

There was no atrophy or other change in the external appearance of the spinal cord or on transverse sections through it at cervical, dorsal or lumbosacral levels.

Microscopic: After fixation in formalin, representative sections from all parts of the cerebral cortex and from representative levels of the spinal cord were stained with cresyl-violet, hematoxylin-eosin, by the Neimer method for myelin sheaths and the Bodian and Perdrau silver methods. Serial sections of the basal ganglia and brain stem were prepared in the same way. The cerebellum was divided in a sagittal plane through the mid-vermis and serial sagittal sections of the vermis and entire cerebellar hemisphere of both sides were stained as indicated. Holzer stains were also done on sections of the cerebellum and the medulla.

In the *cerebral cortex* there were diffuse non-specific senile changes of comparatively small magnitude—loss of cells, occasional small focal clearings, and mild degenerative changes of some of the neurons. These alterations were greatest in the frontal lobes. The Betz cells were present in normal number and condition. Moderate arteriolar sclerosis was everywhere evident. No senile plaques were observed in silver stains and there were no remarkable changes of the neuroglia.

In the *basal ganglia* the principal changes were of the globus pallidus, greatest in its lateral segment. In general there was loss of ganglion cells and of those remaining scarcely any appeared normal. The least affected neurons were pale stained, had undergone complete chromatolysis and many had irregular, deformed outlines with swollen, irregular nuclei. In some, the nucleoli were pale and swollen, and often could not be identified. Many of the cells were loaded with inclusions of granular pigment material which took a gray-green tint in cresyl violet stains, light brown in hematoxylin-eosin. The whole perikaryon was often transformed into this substance in which case the nucleus was no longer visible. Extreme pigmentary degeneration of this kind predominated in the lateral segment of the pallidum and here, especially, the remnants of neurons were greatly shrunken and surrounded by wide, empty spaces (fig. 2). Completely empty spaces, formerly the site of cell bodies, were numerous. In addition there were many small, irregular areas where marked loosening and breakdown of the ground substance had occurred, converting it into lacunae occupied by fibrillar material. There were no fat-granule cells in these areas. The total effect was an *etat lacunaire* of fine calibre. In the pallidum there was an increase of neuroglial nuclei of all types proportionate to the amount of neuronal degeneration. Many of these cells, both microglial and astrocytic, contained granules of pigment like that in the neurons. The caudate and lenticular nuclei and the thalamus were the site of disseminated arteriosclerotic changes. The arteries and arterioles were everywhere greatly thickened and had become hyalinized; the capillaries were fibrosed. Around the sclerotic vessels an *etat cribre* had developed with perivascular focal loss of neurons, rarefaction of the ground substance, and occasional small collections of macrophages and fat-granule cells. Here and there a thrombosed artery was

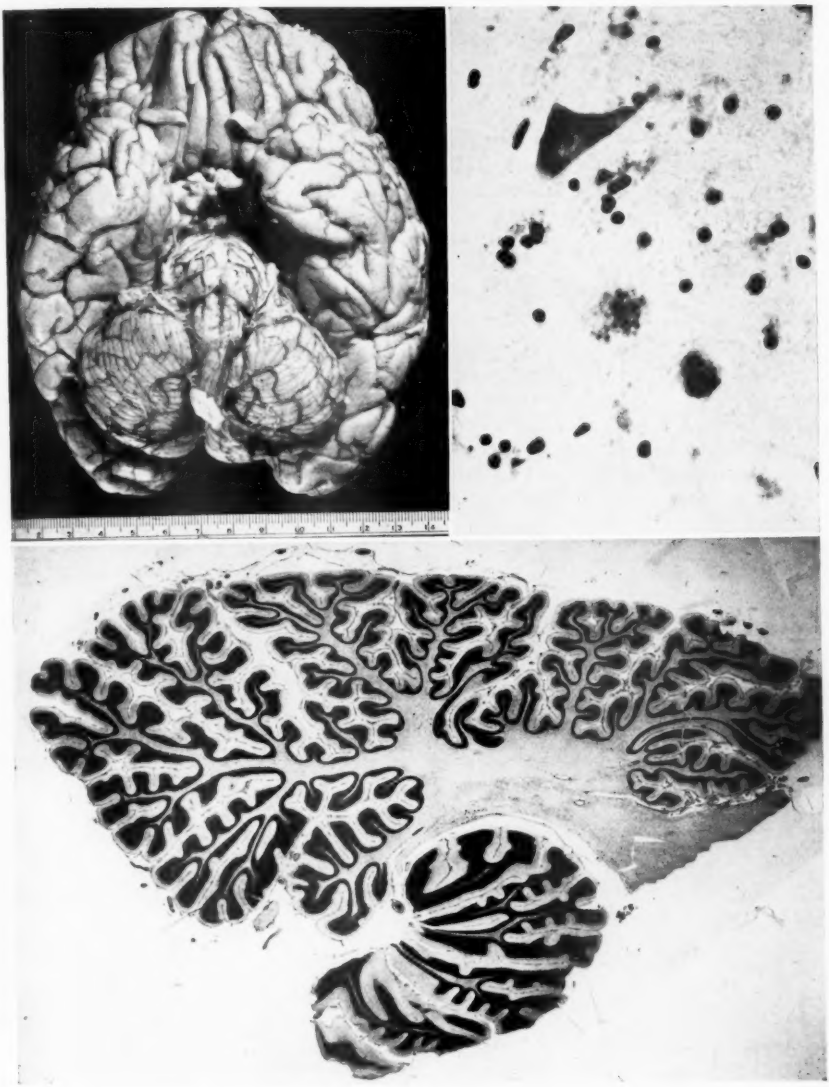

FIG. 1. (*Upper left*). Brain of Case 1. Note the well developed and well preserved pars basilaris of the pons middle cerebellar peduncles and olivary eminences. There is only moderate atrophy of the cerebellum.

FIG. 2. (*Upper right*). Globus pallidus. Cresyl violet. One comparatively normal neuron above and two exhibiting extreme pigmentary atrophy below.

FIG. 3. (*Bottom*). Sagittal section through the left cerebellar hemisphere. Cresyl violet stain. Observe the greatest atrophy in the antero-superior lobules, less in the postero-inferior portions.

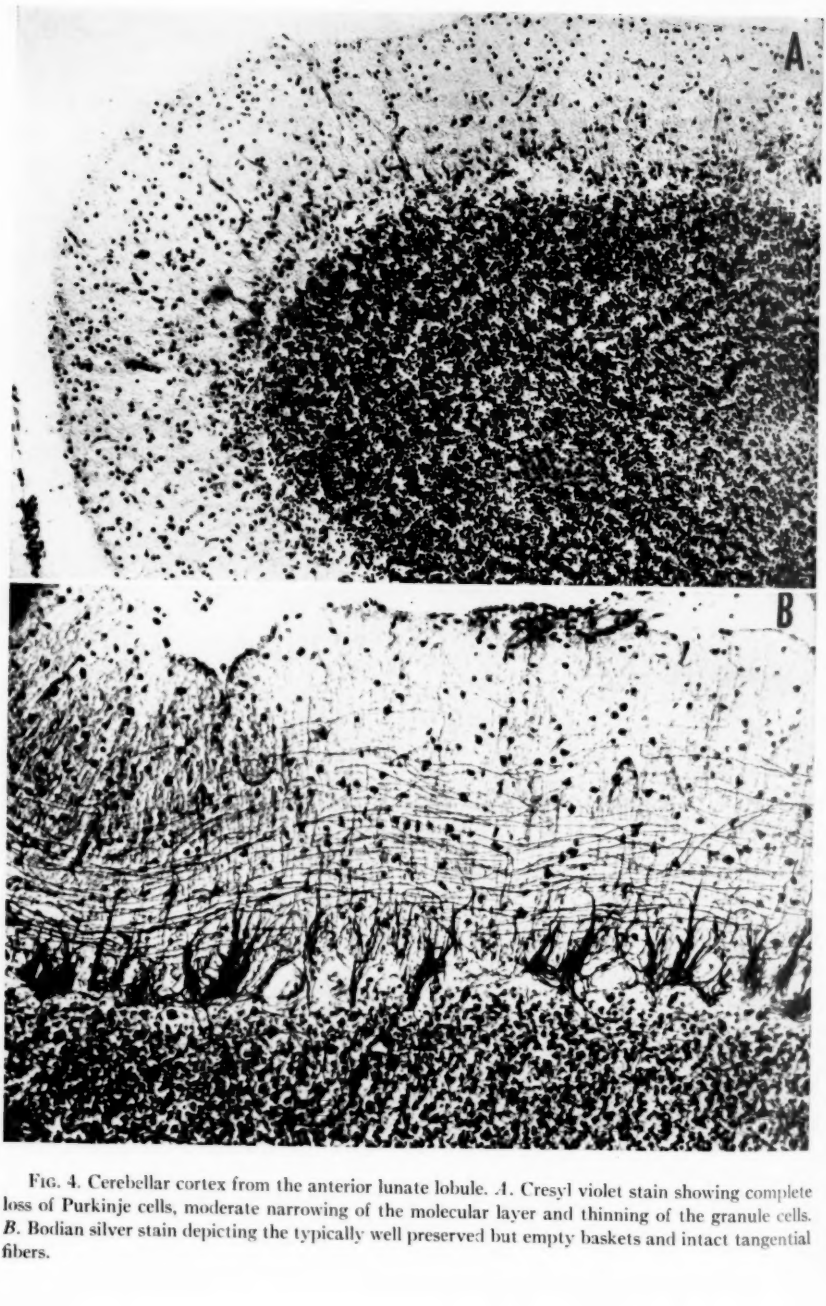

FIG. 4. Cerebellar cortex from the anterior lunate lobule. *A*. Cresyl violet stain showing complete loss of Purkinje cells, moderate narrowing of the molecular layer and thinning of the granule cells. *B*. Bodian silver stain depicting the typically well preserved but empty baskets and intact tangential fibers.

encountered and an occasional, minute and ancient infarct, represented by a linear scar of mesodermal and neuroglial origin in which there lingered a few macrophages containing old blood pigment. The neuronal changes in the basal ganglia, including the pigment content of the cells, did not exceed what might be expected in a brain of this age, except for the globus pallidus. In myelin sheath stains of this area there was loss of some fibers and degeneration of others in the outer segment of the globus pallidus together with thinning and pale staining of the ansa lenticularis. Aside from this the myelin pattern was normal.

It was in the *cerebellum* that the most notable changes were encountered and here they were of quite a different kind from the vascular damage seen in the lenticular nuclei. The salient feature of the cerebellar lesion was a systematic neuronal degeneration and deficiency involving the cerebellar cortex and resulting in selective cortical atrophy (fig. 3 and 4). The most obvious indication of this process was a widespread loss of Purkinje cells. In the more affected regions entire folia were completely devoid of these elements; in less affected areas occasional single cells or even rows of four or five might be found. The surviving Purkinje cells, for the most part, were more or less severely degenerated, showed shrinkage and pyknosis of both cytoplasm and nuclei and sometimes vacuole formation in the cytoplasm. Unlike the neurons of the globus pallidus, there was no pigment accumulation in the Purkinje cells. The other components of the cerebellar cortex were also affected, more or less in proportion to the loss of Purkinje cells. The granular layer was thinned from reduction in the number of its cells and the molecular layer reduced from three-fourths to two-thirds of its normal width. The small stellate cells and the basket cells of the molecular layer, however, were present in normal number and were intact. In silver preparations (Bodian) there was no deficiency of climbing and mossy fibers, the tangential fibers were well preserved, and there were complete rows of empty and, as it were, collapsed baskets, so typical of parenchymatous cortical cerebellar atrophy (fig. 4*B*). In Holzer stains there was no fibrillary gliosis in the molecular or granular layers and none in the region of the prominent layer of Bergmann, indicating that the apparent increase in the number of these glial nuclei was not the result of hyperplasia but merely the effect of loss of neighboring Purkinje and granule cells.

The cortical atrophy was not uniform in all parts of the cerebellum but was selective for more or less definite anatomical subdivisions. In the vermis the lobulus lingulae, centralis, culminus, clivus, tuberis and pyramidis were severely affected while the uvula and nodulus were almost completely spared. In the hemispheres the lobulus lunatus anterior and lunatus posterior were most severely involved, the lobulus postero-superior and postero-inferior less so, while lobulus biventralis and tonsil were almost untouched. These regional differences are illustrated in fig. 3 and in drawings projected from the serial sections in fig. 5, where it is seen that the atrophy of the folia of the superior and anterior portions of the vermis and the hemispheres is so great that the sulci are grossly widened. The drawings are schematic and the differences from lobe to lobe were not as sharp as might appear. Rather there was a graded involvement, greatest in the superior anterior parts of vermis and lateral lobes, decreasing progressively in a posterior and inferior direction. The degree of atrophy did not always conform to the anatomical boundaries of component parts of the cerebellum. Thus, in the medial part of the left lobulus postero-superior, the superior half of the lobule showed very severe atrophy, resembling that of the posterior lunate lobule lying just above it, while the inferior half, much less atrophic, was like the lobulus tuberis inferior to it. It should be noted also that the difference in degree of cortical atrophy between the severely affected lobulus lunatus posterior and the less atrophic lobuli posterior superior, posterior inferior and biventralis, lay more in the degree of narrowing of the molecular layer and thinning of the granular layer than in the difference in loss of Purkinje cells which were very sparse in the latter locations also.

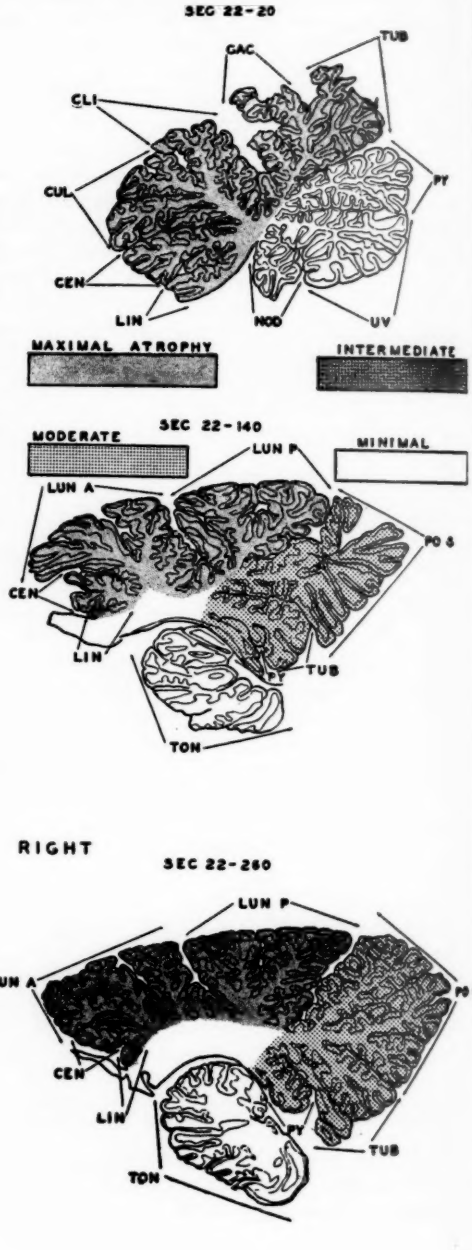

FIG. 5. Projected drawings of serial sagittal sections of the vermis and the cerebellar hemispheres. The sections are arranged in a medial to lateral series from the upper left to the lower right corner of the plate. They illustrate the systematic topography of the atrophy throughout the vermis and the hemisphere, with greatest involvement in the anterior and superior lobules of both, decreasing posteriorly and inferiorly. The degree of atrophy is indicated by differences in shading. The small solid black area in section 23–20 represents the only region of vascular damage (infarction) found anywhere within the cerebellar cortex.

Key:

LIN — lobulus lingula
CEN — lobulus centralis
CUL — lobulus culminis
CLI — lobulus clivi
CAC — lobulus cacuminis
TUB — lobulus tuberis
PV — lobulus pyramidis
UV — lobulus uvulae
NOD — lobulus noduli
TON — lobulus tonsillaris
LUN A — lobulus lunatus anterior
LUN P — lobulus lunatus posterior
Po S — lobulus postero-superior
SLUN 1 — lobulus semilunaris inferior
GRA A — lobulus gracilis anterior
GRA P — lobulus gracilis posterior
BIV — lobulus biventralis
FLO — lobulus flocculi

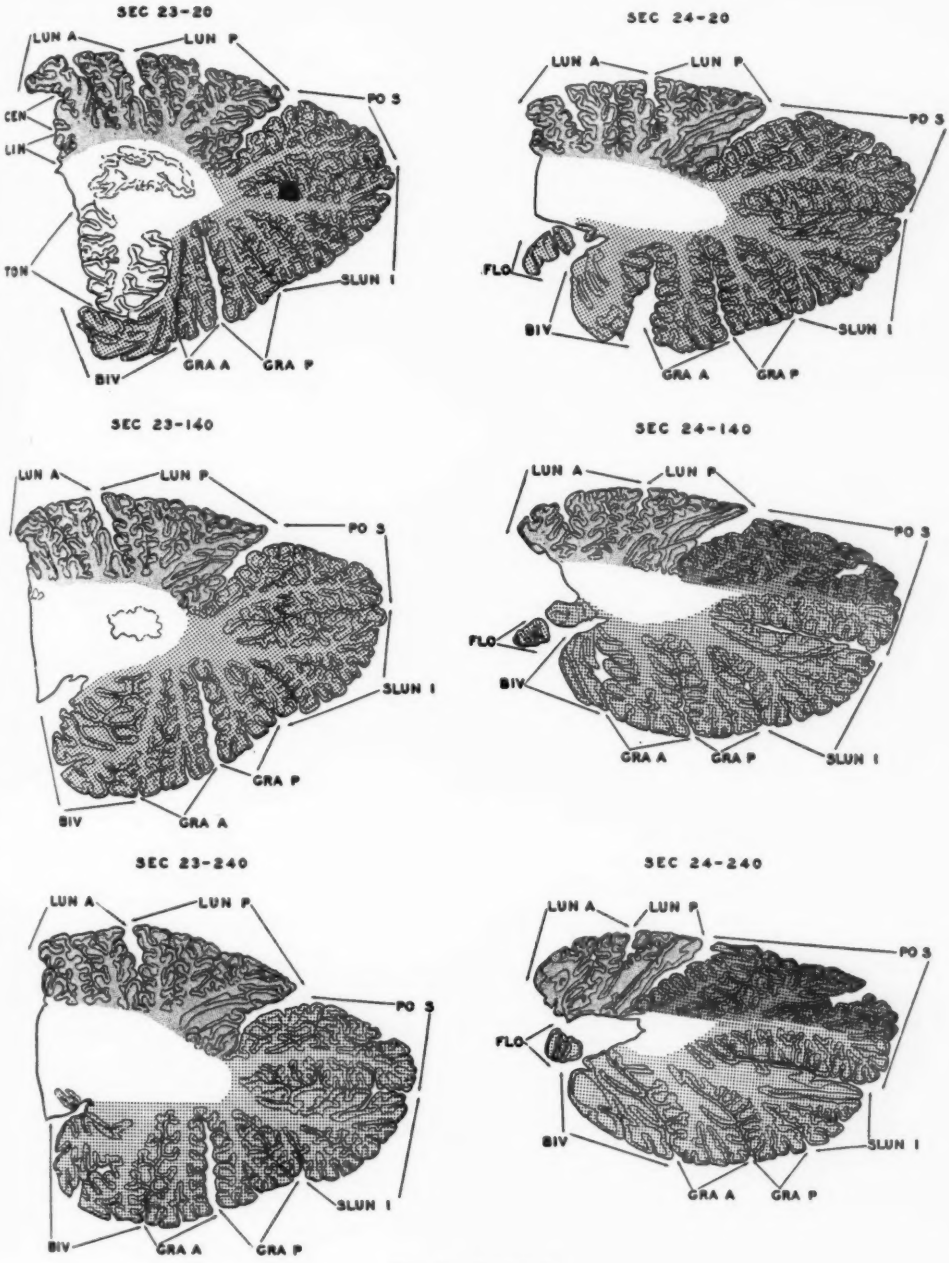

FIG. 5.—*Continued*

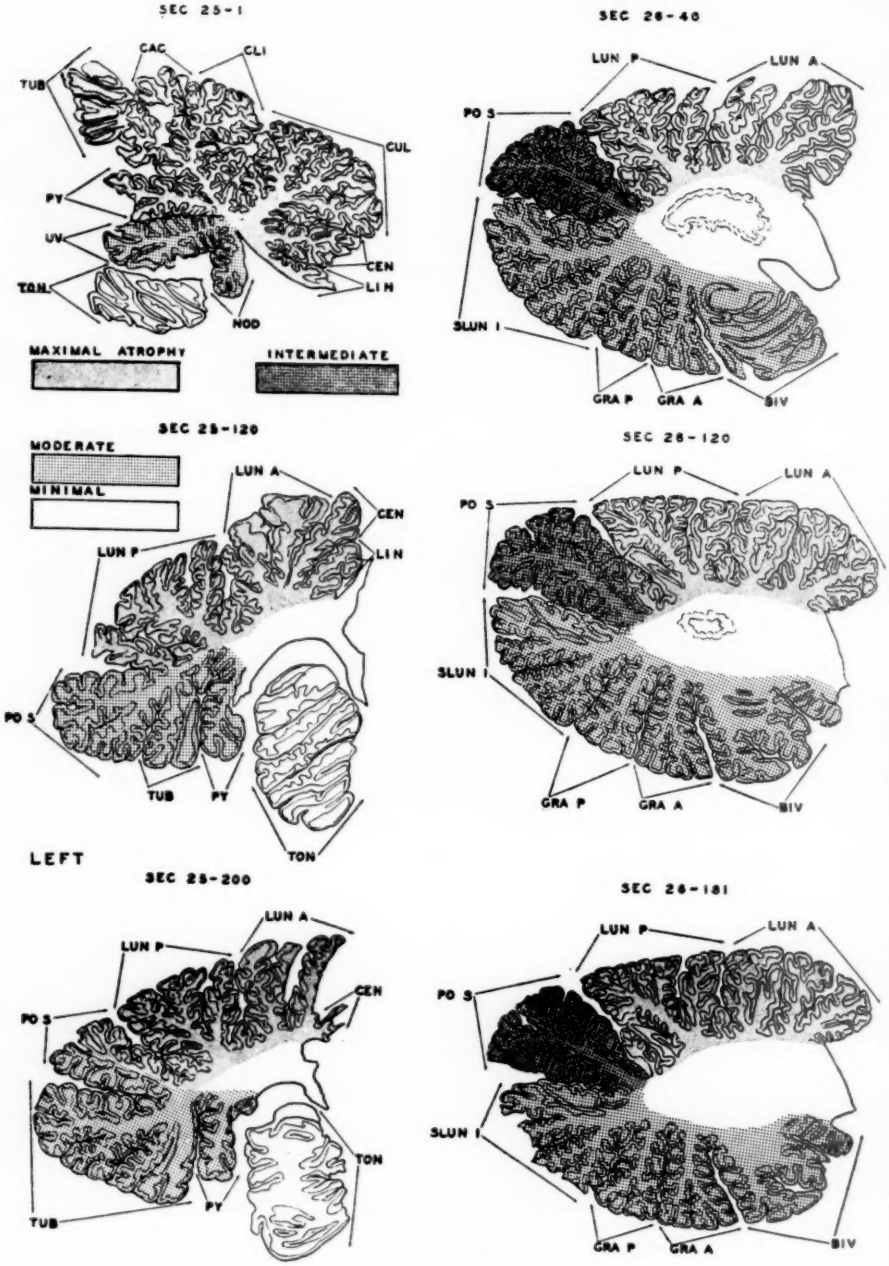

FIG. 5.—*Continued*

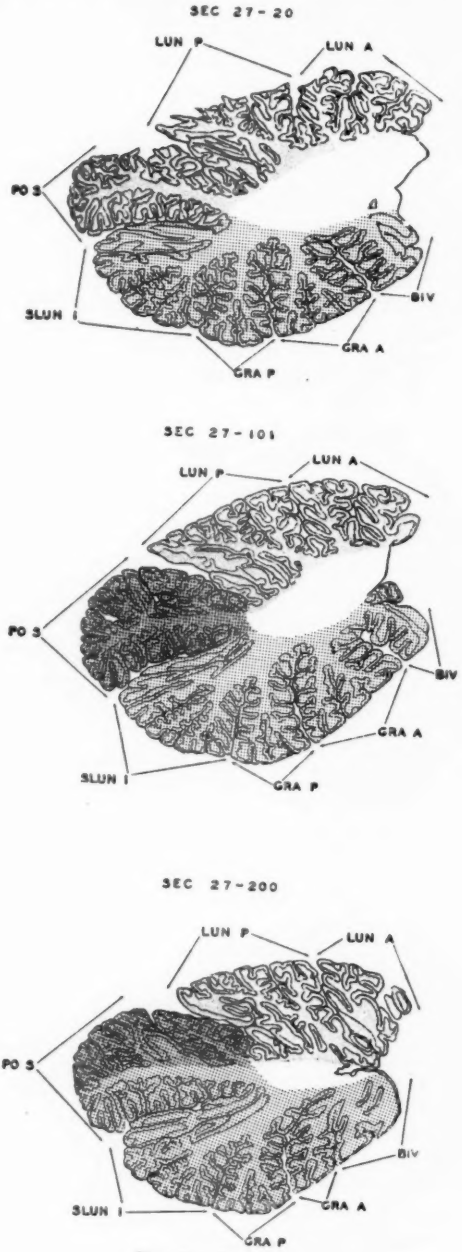

FIG. 5.—*Concluded*

Among the deep cerebellar nuclei, it was the dentate that showed the most definitive changes. All of the neurons were either shrunken and deeply stained or pale, and, in both instances, presented a degree of pigmentary degeneration far in excess of any mere senile change (fig. 6*A*). Furthermore, there was a striking increase of astrocytic nuclei within the gray matter of the dentate. These alterations were considerably less in a small medial and oral portion of the dorsal fold of the dentate and in a somewhat larger area of the medial portion of the ventral fold than elsewhere in the nucleus (fig. 8). In Holzer stains there was extreme isomorphous fibrillary gliosis which involved the whole of the convoluted gray matter and was even denser in the central white core, the hilus and the fleece of the dentate (fig. 6*B*). There was only moderate proliferation of neuroglial fibrillae in the deep white matter and in the axial cores of the white matter of the foliae.

As elsewhere in the nervous system, there was well marked arterio- and arteriolar sclerosis in the cerebellum but extremely little actual vascular damage. In the dentate nucleus a cribriform state had developed, similar to but not as advanced as that in the lenticular nuclei. Within the cerebellar cortex there was only one minute area of old infarction, 1.0 to 2.0 millimeters in diameter located along the sulcus horizontalis magnus, involving a few foliae of the lobuli semilunaris inferior and postero-superior. Here the molecular layer was absent and the granule cells had disappeared, leaving only a collection of large vesicular glial nuclei. This lesion was so small that it could have had no conceivable part in producing cerebellar symptoms. The contrast afforded by the totally different appearance of this small vascular lesion as compared with that of the atrophic cerebellar disease gave a clear demonstration that the latter was not vascular in origin.

In the brain-stem the usual sclerotic changes of the vessels were encountered and, in the pons, an occasional thrombosed artery. In the nuclei pontis were a few small focal areas of neuronal outfall and gliosis, the result of old infarctions. Aside from this insignificant damage, the pontine nuclei were intact and gave no evidence of atrophy. The arcuate nuclei were unaffected. The substantia nigra, nucleus ruber and reticular formation of the brain stem were normal for the patient's age. In myelin stains the superior middle and inferior cerebellar peduncles were well preserved as was the case also with the transverse pontine fibers, the posterior longitudinal bundle, the olivo-cerebellar tracts, and the arcuate fibers.

The inferior olives in cresyl-violet and myelin stains appeared grossly normal, full, well developed, and not at all atrophic. Cellular stains, however, showed neuronal damage in these structures. In some parts of the olives there was appreciable loss of cells and all of those present exhibited cell atrophy and pigmentary degeneration such that, in the more severely involved regions, nothing remained of the ganglion cells but a shrunken collection of pale, yellow-green pigment granules (fig. 7*A*). Furthermore, there was great increase in the number of astrocytic nuclei present in the convoluted gray matter of the olives. In Holzer stains a dense fibrillary gliosis of the gray matter, the hilus and the capsule was outstanding (fig. 7*B*). The olivary alterations were similar to those of the dentate nuclei, and in the olives, too, there were well defined, symmetrical topographical differences in the degree of involvement (fig. 9). This was greatest in the rostral pole of the main olivary nuclei and in the dorsal assessory olives where the cell loss amounted to at least one-half. Next in order were the dorsal leaves of the main olivary nuclei and the greater (dorsal) portions of the medial accessory olives. There was considerably less damage of the ventral leaves of the main olives. The only relatively normal olivary neurons were a small group of from 10 to 25 cells located in the ventral-most portion of the medial accessory olives.

Sections of the spinal cord at cervical, dorsal and lumbo-sacral levels were normal. In particular, there was no demyelination or atrophy in the region of the spino-cerebellar tracts or the posterior columns of the spinal cord. The cells of the columns of Clarke and those of the nuclei gracilis and cuneatus were likewise intact.

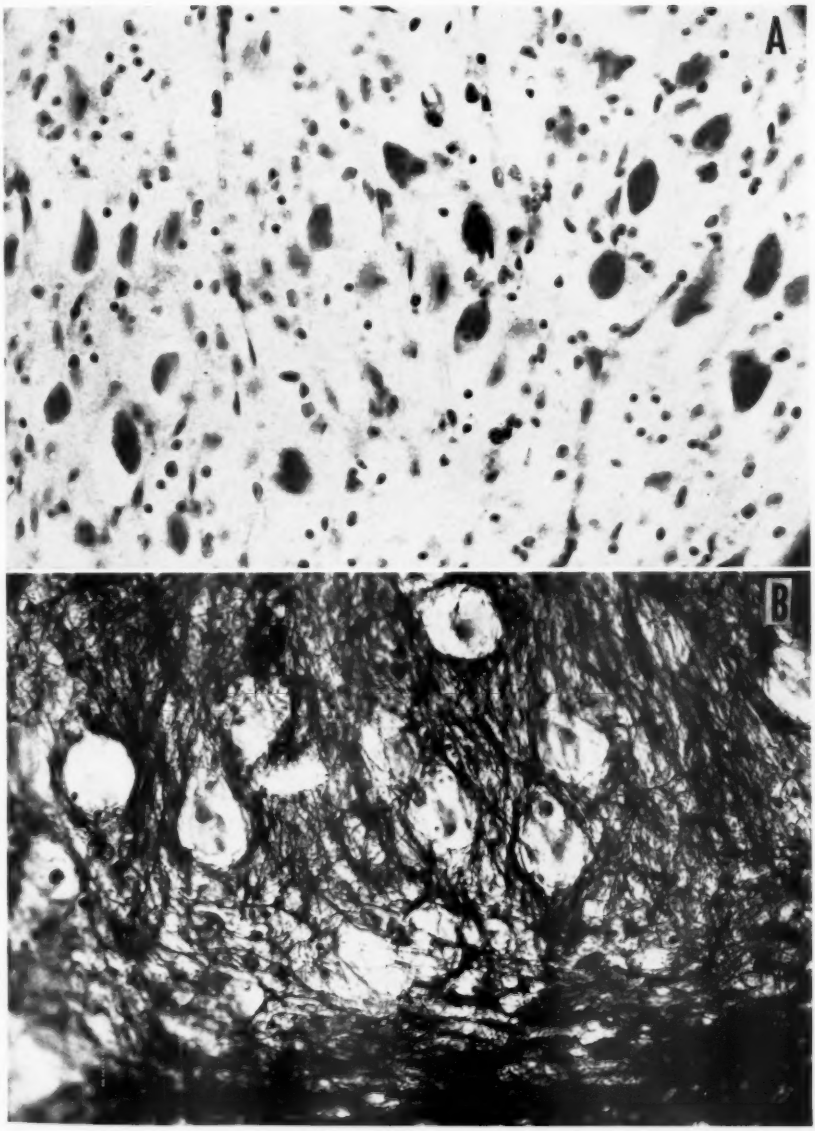

FIG. 6. Dentate nucleus. *A*. Cresyl violet stain. Note pigmentary degeneration and atrophy of neurons and increase of neuroglial nuclei. *B*. Holzer stain, showing dense fibrillary gliosis of the convoluted gray matter of the dentate.

Case 2. L. W., a widow 87 years of age, a cousin of Case 1, was examined on October 20, 1945. The history as obtained from the patient and her son indicates that for at least 25 years

FIG. 7. Superior leaf of the main olive. *A*. Cresyl violet stain showing loss and pigmentary degeneration of nerve cells and gliosis. *B*. Holzer stains of the olives. Fibrillary gliosis including the nuclear gray ribbon, the capsule and the hilus.

she had experienced frequent falls, occasionally resulting in fractures, but that definite gait disturbances did not appear until she was in her seventies, some 12 to 15 years before. The incoordination in her gait developed gradually and became steadily worse through the years. As recently as 8 years ago she could walk for moderate distances with the help of one person but had finally become so unbalanced that she required support on both sides to walk at all. She could still take a few steps alone across a room by holding to the furniture and could climb and descend a stairway with the aid of the stair-rail. Speech was first affected several years after the difficulty in walking began and, like the latter, had become slowly

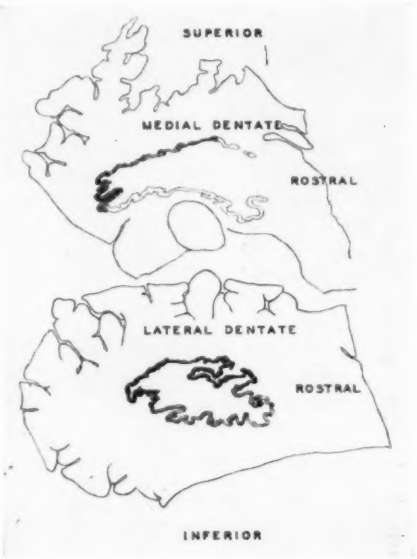

FIG. 8

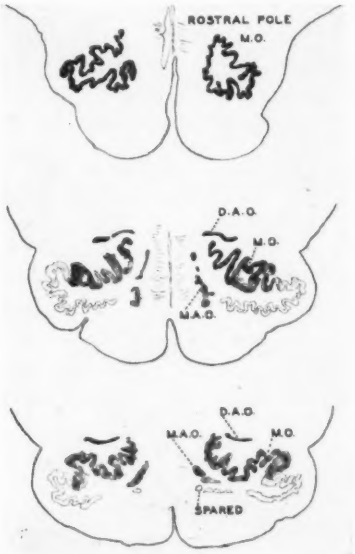

FIG. 9

FIG. 8. Projected drawing of the dentate nucleus illustrating the distribution of the degenerative neuronal changes. Heavier shading indicates greater degeneration. Note that the dorsal fold is more affected than the ventral and that there is greater involvement laterally than medially.

FIG. 9. Projected drawings of the olives showing the topography of the degeneration. Greater degeneration is indicated by greater depth of shading. The rostral pole of the main olive and the dorsal accessory olive are most severely involved, the dorsal leaf of the main olive and the medial accessory olive less so, the ventral leaf of the main olive still less. Only a small part of the ventral portion of the medial accessory olive is spared. M.—main olive; D.A.O.—dorsal accessory olive; M.A.—medial accessory olive.

worse. She was able to make herself understood to her immediate family. It was only within the preceding few years that she had shown awkwardness in the use of her hands. She could dress herself, however, and feed herself without a great deal of spilling. Her family was sure that her mental faculties were still excellent. Not only was her memory clear for the distant past but she also observed and recalled current events in the family and neighborhood life. She knew the season's baseball scores and often put the younger members of the family to shame by her fund of information when listening to "quiz programs" on the radio.

When she was examined it was observed that her stance was on a wide base and she swayed a great deal in all directions, equally with the eyes open or closed. She would have

fallen without support. Even when held up on both sides she walked with her feet far apart, lurched and fell in all directions, and exhibited dysmetria of the lower extremities by placing her feet too far forward or too far to the sides with almost every step.

Ocular movements were full except for restriction of conjugate upward gaze. There was moderately coarse, sustained horizontal nystagmus in lateral gaze to either side and similar vertical nystagmus in upward gaze. Dysarthria was so great that it was frequently impossible for the examiner to understand the words. The speech impairment was in part dependent upon slurring of consonants, in part upon a slow, jerky, ataxic rhythm of speech, typically cerebellar in quality. Alternating tongue movements were executed slowly but there was no weakness of the tongue or other signs of bulbar palsy and the jaw-jerk was not increased.

When the patient was sitting motionless a coarse ataxic tremor of the head was frequently evident and similar static tremor of either arm or hand when it was held against the face or even when it lay supported in her lap. Ataxia was extreme in the heel-to-knee test on both sides and there was some, but much less, incoordination in the finger-to-nose test bilaterally with the terminal intention tremor. Adiadokokinesia was also very marked in movements of all extremities and the Gordon Holmes rebound phenomenon was present in both arms. Hypotonia was present in both legs and in the left arm.

Strength of the arms, legs and trunk was excellent in all movements. The tendon reflexes were all normally active and equal and no pathological reflexes could be elicited. Vibratory sensation was lost in the lower extremities but position sense was intact and there were no other sensory disturbances.

Case 3. C. W., the son of L. W. (Case 2) now 65 years of age was examined May 2, 1948. Except for known hypertension for some years he had been well until the onset of his nervous disorder at the age of 60. In 1942 he began to notice a tendency to stumble especially when going down stairs, but it was only in 1944 that his instability became very great. It had increased since then until he was now able to walk only with the aid of a cane. He had fallen a number of times especially when trying to turn. Soon after his gait disturbance became evident he began to have difficulty also with movements of his hands and arms. His handwriting which had previously been very legible became laborious and indistinct and he now printed by preference. He spilled his food, fumbled when he buttoned his shirt or tied his cravat, and found it very difficult to shuffle cards but could still do so. In 1945, when visiting a dental laboratory, he found that he could not say "colloid" and his speech had deteriorated progressively ever since. In the same year he developed double vision when looking to the left. This, he thought, came on gradually and had remained unchanged. He had had no paresthesias or pain in the legs or arms. He was totally incapacitated for work but read and listened to the radio a great deal. Both he and his family considered that his memory was at least normal for his age.

The gait and stance were on a very wide base. When walking with a cane he swayed and rolled and showed marked hypermetria of the legs in taking every step. He tended to fall forward when standing with his base somewhat reduced. There was no Romberg sign. There was considerable dysmetria and the wildest ataxia in the heel-to-knee. Adiadokokinesia was great in all extremities. A suggestion of hypotonia was felt in the arms, none in the legs. Slight static tremor of the head and of the arms at rest was sometimes seen. The speech was typically scanning, somewhat explosive and with marked slurring of consonants but he could usually make himself understood. There was definite horizontal nystagmus on lateral gaze in both directions and rotary nystagmus on looking upward. No strabismus could be detected. Strength of the arms and legs was good in all muscle groups, the tendon reflexes were all normally active and equal, the plantar responses flexor and no pathological reflexes

were elicited. Sensation, notably that for position and vibration, was normal. He was alert and interested. His memory appeared to be intact and he gave the examiner a long and accurate resume of what several news commentators were saying about the Republican primary in Ohio.

Genealogy (See fig. 10).

Generation I. While both James F. (*I*–J.F.) and his wife, Ellen T., (*I*–E.F.) came of large families, little is known of their siblings. So far as the information goes there was no evidence of nervous disorder in any of them. Ellen F. died at 69 without showing symptoms. James F. died at 86. He walked with a cane in the later years of his life. This was attributed to "rheu-

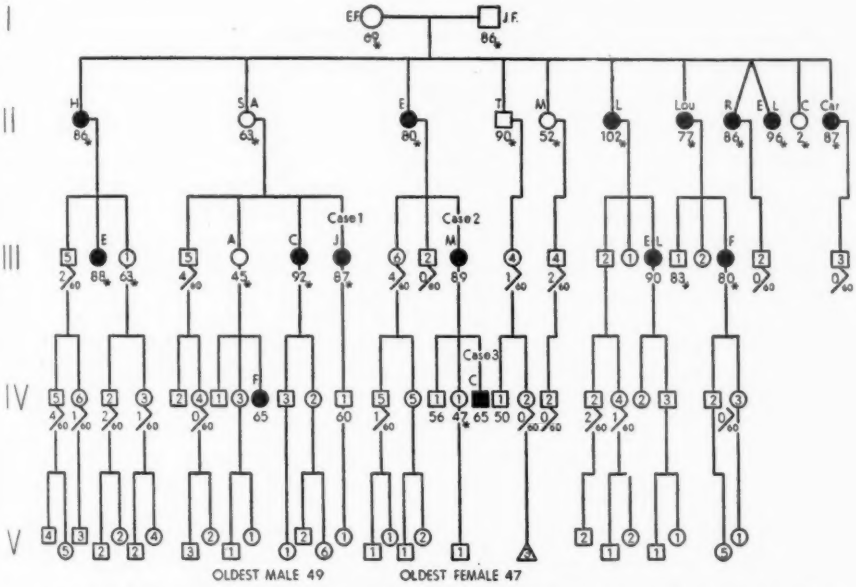

FIG. 10. Pedigree of the F———family. Females are indicated by the conventional circles, males by squares. To conserve space and for greater clarity unaffected members of the several generations and families are grouped in a single symbol with the number of individuals placed within the symbol except in those instances where an unaffected person has transmitted the disease. The number of individuals who were known to have reached an age of 60 or more are shown beneath the symbols ($n > 60$). The number under symbols for single individuals is the age when known. Numbers with asterisks are the ages at death, the unmarked numbers the ages in 1948.

matism." Members of the third generation who are still living and knew him well are certain that he did not have the same affliction as the aunts of generation *II*. He was descended from Irish, Welsh, English and Scotch ancestors who had settled early in Pennsylvania. There is nothing in the family records to suggest the presence of the disease in his antecedents. Ellen F. was born in England. Almost nothing is known of her forebears. There was no consanguinity in this marriage or in those of subsequent generations, and none of the consorts of members of any generation were known to have symptoms of ataxia.

Generation II. Of the 10 daughters born to James and Ellen F., 7 developed well marked symptoms of what came to be known in the family as "the trouble," that is, increasing and

finally severe disorders of gait with impairment of speech. Characteristically the first warning of the oncoming disease was difficulty in descending stairs. They were observed to do this "sideways." In all of them the symptoms appeared late, after the age of 65, and it will be noted that of the three daughters who did not show the disease one (*II*–C) died in infancy and the other two, (*II*–SA) and (*II*–M) died at ages 63 and 52 respectively, too young to be expected to show symptoms. One of these (*II*–SA) carried the gene and transmitted it to two of her daughters. The affected women of this generation were notable also for their longevity, 6 of them living well beyond 80 years. The only male in the family (*II*–T) never showed symptoms although he lived to be 90, nor did he transmit it to any of his 4 daughters, one of whom is still living at 78.

Generation III. In this large generation of 46 members to which Cases 1 and 2 (*III*–J and *III*–M) belong, 6 members are known to be afflicted (*III*–E, *III*–C, *III*–J, *III*–M, *III*–EL, *III*–F). These are all females, all showed their first signs at about the age of 70 and, like their predecessors of generation *II*, all lived to be 80 or past. An inspection of the pedigree for this generation shows that of the 7 affected daughters of generation *II*, 4 transmitted the disease to a daughter of generation *III*. The 3 affected females of generation *II* who did not pass on the disease either had no offspring (*II*–EL) or had only sons who died under the age of 30 (*II*–R and *II*–CAR). None of the males had the disease but it is of interest that 7 of them, from three different families, were red-green color blind.

Generation IV. Although this is the largest generation of all, made up of 67 individuals, only two are known with certainty to have the disease, (*IV*–F) and (*IV*–C, Case 3). Here the circumstances are somewhat different than in generations *II* and *III* in that the disorder appeared at a somewhat earlier age and that it appeared in a male (*IV*–C), the son of an affected female (*III*–M). The affected female was the daughter of an unaffected mother (*III*–A), but again, this woman (the mother) died at 45 before she might be expected to show symptoms.

Generation V. None of the members of this generation have as yet developed symptoms, but the oldest male is only 49, the oldest female 44 years of age.

DISCUSSION OF NEUROPATHOLOGIC FEATURES

In any biological problem where heredity is a consideration it is necessary that the phenotype in question be definite and identifiable. In my opinion this condition is fulfilled by parenchymatous cortical cerebellar atrophy if both the clinical and pathological characteristics of any given case are taken into account and certain criteria insisted upon. The symptoms and signs of cerebellar disorder as they are seen in the disease are, of course, not in themselves specific, but late onset in the fifth decade or after, a prolonged course over some years, and slow progression are the clinical features that are characteristic if not essential. The pathological changes in the brain are much more definitive and there is general agreement among almost all writers who have studied and reported upon cases of this kind that, in its essentials, parenchymatous cortical cerebellar atrophy may be considered a distinct type of pathological reaction in the cerebellum, distinguishable from the cerebellar aplasias, ordinary acquired lesions, atrophies secondary to extensive destruction of the cerebrum, and from certain other intrinsic cerebellar degenerations such as olivo-ponto-cerebellar atrophy. This point of view is well expressed by Scherer (1933) in his

exhaustive study of cerebellar diseases. The pathological picture of the present case is described in some detail in order to emphasize again the individual stamp that the disorder bears and to identify it as an example of parenchymatous cortical cerebellar atrophy. In addition, the material displays associated changes of the dentate nuclei, the olives and the globus pallidus deserving of attention and comment.

A special and constant kind of atrophy of the cerebellar cortex is the crucial and indispensable part of the pathological syndrome. The atrophy is always even and diffuse and always most obvious in the Purkinje cell layer which is usually completely obliterated in the areas most affected. While the granular layer is often thinned in the severely involved parts, it is never completely destroyed and may be entirely unaffected. Similarly, the molecular zone shows comparatively less degeneration. It is reduced in width in many instances but the small stellate cells and the basket cells within it are intact. This is in keeping with the striking preservation of their dendritic baskets, emptied of Purkinje cells, that has become a sort of hall-mark of this cerebellar lesion. Notable also is the preservation of other afferent cortical elements such as the mossy and the tangential fibers. Within the cortex little, if any, neuroglial reaction accompanies the degeneration of the parenchyma, either in the form of proliferation of gliocytes or formation of glial fibers. It would appear that the undue prominence of the astrocytes of the Bergmann layer, evident in this case as in others, is to be attributed to the mere uncovering of these nuclei by the atrophy, rather than to true hyperplasia as has often been stated.

The distribution of the cortical atrophy has proved to be no less a characteristic of the disorder than is its nature. In a few of the cases the cortical changes have been approximately equal in all of the cerebellar folia. Most reports, however, have emphasized the accentuation of the process in the superior and anterior parts of the vermis and of the lateral lobes, with a somewhat gradual shading-off in degree of atrophy caudally and ventrally both in the vermis and the hemispheres. Such a disposition was encountered in this case also. The selection of the vermis and the anterior lobe in general has led a number of writers, from Marie, Foix and Alajouanine on, to postulate that the degeneration is selective for the phylogenetically older portions of the cerebellar cortex, that one is dealing with a paleocerebellar atrophy. Logical and satisfying as this idea might be in explaining the distribution of either an hereditary or acquired atrophy, the facts are that it is by no means the case. If the exact allocation of the changes in this case is considered in the light of present knowledge of cerebellar ontogeny and phylogeny as worked out by Ingvar (1928), Larsell (1937) and Dow (1942), it becomes apparent that in location and in degree there is no observance of generally accepted paleo- and neo-cerebellar boundaries. The most affected region, to be sure, is the anterior lobe (composed of lingula, lobulus centralis, and culmen, and lobuli lunatus anterior and posterior) which

is to be considered paleocerebellar since it receives principally spino-cerebellar afferents and probably some vestibulo-cerebellar fibers as well. There is also, however, obvious involvement of lobuli postero-superior, postero-inferior and biventralis, homologues of the neo-cerebellar lobulus ansiformis, having cortico-ponto-cerebellar afferent projections. Finally, of the parts of the cerebellar cortex least involved or "spared," one, the nodulus, is thought to be the oldest of the paleo-cerebellar structures; the other, the tonsil, is regarded as neocerebellar. Courville and Friedman (1940) have also noted and emphasized this lack of correlation and are quite right when they state that a *coup de grâce* has been given to the conception of phylogenetic regional atrophy in parenchymatous cortical cerebellar atrophy. It should be mentioned, too, that neither does the atrophy follow strictly the gross anatomical dividing lines or parts of the cerebellum. Thus, the lobulus postero-superior was very atrophic in its upper half, much less so in its lower.

The absence of changes in certain parts of the cerebellum and in certain accessory structures is also an important item in the total picture presented by parenchymatous cortical cerebellar atrophy. It can be said that the deep medullary white matter and even the branches of white matter in the lamellae, are never affected to any considerable degree. For this reason the gross atrophy is not visibly very great and the weight of the cerebellum is usually only moderately reduced. The cerebellar peduncles, too, are intact grossly and microscopically. There is characteristically no significant damage to the nuclei pontis or the transverse pontine fibers, and no advanced or gross atrophy of the inferior olives and the olivo-cerebellar tracts, nor of the arcuate nuclei or fibers.

The characteristics just enumerated are the essential and invariable ones and to them the present case conforms in every particular. Less constant changes have been noted in the inferior olives by Marie, Foix and Alajouanine (1922), de Haene (1937), Hall, Noad and Latham (1941), Weber and Greenfield (1942), and others, and in the dentate nuclei by Parker and Kernohan (1933), and Richter (1940). In this case the olives and dentate nuclei are implicated in a degenerative process that is clearly the same in both and is distinguished by advanced, pigmentary degeneration of neurones, loss of many, and high grade astrocytic fibrillary gliosis without gross wasting of the structures themselves. Several writers have expressed the belief that the olivary changes are simply secondary to those of the cerebellar cortex, representing "trans-synaptic" degeneration at a distance. So it seems to me, especially in view of the mutual topographical relations that exist in this case between the changes in the olives and those in the cerebellar cortex. The best information available on olivo-cerebellar localization and connections is that furnished by the experimental work of Brodal (1940) on rabbits and cats and by Holmes and Stewart (1908) from clinical studies in man. The data from these sources indicates that the

most anterior and superior portions of the cerebellar vermis and hemispheres receive projections from the dorsal accessory olive and the rostral pole of the main olive. In the brain of this case it is just these two regions of cerebellum and olives respectively that show the greatest changes. Similarly, the more affected postero-superior and postero-inferior lobules are considered to be in relation to the more affected dorsal leaf of the main olive, while the less affected biventral lobule and tonsil are thought to connect with the ventral leaf of the main olive, which here is less affected than the dorsal leaf. According to the available evidence, the inferior vermis receives its olivo-cerebellar afferents from the medial accessory olives. On this assumption the degeneration found in the dorsal portions of the medial accessory olives may be considered to reflect the atrophy present in clivus, tuber, pyramis and uvula. The groups of intact neurons present in the ventral portions of the medial accessory olives, the only normal areas remaining in the olivary complex, suggest that this locus projects to the nodulus, the most nearly normal area remaining in the inferior vermis.

If the effect on the afferent system of the olives is the result of secondary degeneration, it might be expected that similar effects would be encountered as regards the efferent projections of the cerebellar cortex upon the dentate nuclei. The state of the dentate nucleus in this case indicates that this is so. The nature of the changes, like those in the olives, is consistent with a slow secondary degeneration and sclerosis. Moreover, there are local differences in the severity of the neuronal degeneration in the dentate which may correspond with reciprocal topographical relationships between the dentate and the cerebellar cortex. In general the dorsal fold of the dentate is more affected than the ventral fold. Within the dorsal fold only a small frontal and medial portion shows relative sparing, while in the ventral fold a larger medial segment is spared frontally and caudally. One might infer from this that the cortex of the superior vermis and the superior surface of the hemispheres, representing in large part the paleocerebellar anterior lobe, projects upon the dorsal fold of the dentate while that of the inferior vermis and inferior surface of the hemispheres, including the homologues of the neocerebellar lobuli ansiformis (Crus II) and paramedianus, connect with the ventral fold. The tonsil, being the least affected part of this area, is perhaps in relation with the less affected medial portion of the ventral fold. This scheme does not, however, correspond well with the conclusions of Brun (1917) who, on the basis of the state of the dentate in cases of neocerebellar aplasia, thought that the caudal and ventro-lateral frontal portions of the dentate were neocerebellar, the dorso-medial frontal portion paleocerebellar or with those of Demole (1927) who considered that the dorso-median part of the dentate is connected with the vermis, the ventro-lateral portion with the hemispheres.

The pathological details have been reviewed and described at some length primarily to support the thesis that parenchymatous cortical cerebellar atrophy

is some kind of entity, probably a disease *sui generis* with an individuality that can be recognized with as much confidence as in the case of olivo-ponto-cerebellar atrophy or Friedreich's ataxia. It is confusing and, I believe, erroneous to place such conditions as Hassin's (1934) *sclerotic atrophy of the cerebellum* or Lichtenstein and Levinson's (1946) *cortical cerebellar atrophy: primary circumscribed variety* in the same category. These patchy or localized "panatrophies" with indescriminate destruction of all elements of the cortex and dense neuroglial sclerosis have every appearance of old acquired lamellar necrosis. They have nothing in common with late primary cortical cerebellar atrophy except that both conditions are located in and more or less limited to the cerebellar cortex.

More perplexing and difficult to evaluate are some of the cases of primary degeneration of the cerebellar cortex and the olives such as the often cited ones of Holmes (1907). These I would be inclined to exclude from the group of parenchymatous cortical cerebellar atrophy on the basis of the degree of involvement of the cerebellar white matter and the consequent marked gross atrophy of the organ (weight 58 g.). The example reported by Hänel and Bielschowsky (1915) under the name of *olivo-cerebellar atrophy* can certainly be excluded and is best regarded as an incompletely developed olivo-ponto-cerebellar atrophy. On the other hand the heredofamilial case of Weber and Greenfield (1942) designated by them as *cerebello-olivary degeneration* should, in my opinion, be considered to belong to the group of parenchymatous cortical cerebellar atrophy and the same may be said for the patient of Hall, Noad and Latham (1941) who came to autopsy. These two groups of cases are very similar. The nature and distribution of the intracerebellar cortical changes were typical and it would appear that only the rather striking alterations in the olives has kept them from being regarded as parenchymatous cortical cerebellar atrophy. But as pathological observations on that condition multiply it is becoming more and more apparent that secondary "retrograde" olivary degeneration is by no means uncommon both in the heredo-familial and in sporadic cases. Only if there is gross atrophy of the olives and well marked degeneration of the olivo-cerebellar tracts, need this feature alone place doubt on the diagnosis.

In one respect Case 1 of this report deviates from the usual type; that is, in the presence of marked degeneration in the globus pallidus associated with appropriate extrapyramidal postural changes and tremor in the lower extremities. These are to be looked upon as probably independent of the cerebellar disease. There is enough ordinary arterio-sclerotic damage in the lenticular nuclei to account for them. On the other hand, they may represent a variant of the manifold combinations so frequently met with in the heredo-degenerative diseases of the nervous system. Associated neurological symptoms or signs are not uncommon in the histories of patients with parenchymtous cortical cerebellar atrophy. Thus, Akelaitis (1938) has encountered severe deteriorating

psychosis in three cases. Buchanan, Overhold and Neuberger (1947) reported an association with Pick's disease in which there was progressive dementia and pyramidal signs, and Richter (1940) referred to milder grades of mental deterioration in two of his cases. An early, probable case described by Thomas (1905) had pyramidal tract signs in the legs, and Thorpe (1935) observed major convulsive attacks in two patients. It is of special interest in this connection that extrapyramidal signs (chiefly Parkinsonian) with and without damage in the extrapyramidal motor nuclei have been described in several cases of parenchymatous cortical cerebellar atrophy. Guillain, Garcin and Bertrand (1931) reported a case in which a cerebellar syndrome developed in a patient who had Parkinsonian rigidity. Pathologically there was cortical cerebellar atrophy. The authors state that the basal ganglia and the brain-stem structures were normal but it would appear from their report that these were not adequately examined. Zülch (1936) likewise described an instance of a cerebellar syndrome combined with Parkinsonian rigidity and tremor in which cortical cerebellar atrophy was present pathologically but no changes of other extrapyramidal structures. Case 11 of Hall, Noad and Latham presented slight postural abnormality and rhythmic tremor of the head and fixity of facial expression suggesting Parkinsonism. Recently van Bogaert (1947) has described the brain of a case of hereditary late cortical cerebellar atrophy in which the changes in the cerebellar cortex, the dentate nuclei, the olives and the globus pallidus were almost exactly like those of my Case 1. The pallidal degeneration did not show itself in the clinical syndrome which was purely that of cerebellar disease. The association of extrapyramidal motor disorders is even more striking with olivo-ponto-cerebellar atrophy. Scherer (1933) described four such cases combined with degeneration of the striatum and the substantia nigra. In a case of von Strauffenberg (1918), the Parkinsonian syndrome completely obscured any cerebellar signs, but pathologically there was typical olivo-ponto-cerebellar atrophy, together with extensive damage of the lenticular nuclei. As in my case, the lenticular changes were partly those of focal vascular disease, partly severe pigmentary neuronal degeneration. Ley (1925) reported the case of a patient in whom rigidity and tremor were superimposed upon a cerebellar syndrome. Because he found nothing abnormal in the lenticular nuclei he ascribed the Parkinsonian signs to the cerebellar degeneration, completely ignoring a destructive lesion said to be present in the tegmentum of the mid-brain. Keiller (1926) mentioned that in one of his cases of hereditary olivo-ponto-cerebellar atrophy there was a paucity of cells and fibers in the substantia nigra but no extrapyramidal signs clinically.

MODE OF INHERITANCE

Having presented the reasons for considering parenchymatous cortical cerebellar atrophy a discrete phenotype to which the present material conforms,

we may now return to the main theme of this report, the hereditary nature of the condition. Since the recording of the earlier sporadic and presumably acquired cases, several accounts have appeared, confirmed by pathological examination, first of familial and then of two-generation incidence of parenchymatous cortical cerebellar atrophy. In 1935 Thorpe reported upon two brothers who developed cerebellar symptoms at the ages of 41 and 37 years respectively. The brain of one of them was examined and was found anatomically to be a case of parenchymatous cortical cerebellar atrophy. Later Richter (1940) described the typical pathological changes in a male whose cerebellar disorder began at 47 and whose sister and brother developed similar cerebellar signs at 47 and 55 years respectively. Akelaitis (1938) furnished the first data that indicated dominant heredity. This study was based upon the examination of the brains of two brothers who presented signs of cerebellar disease at 41 and 51 years and whose sister had similar symptoms. The maternal grandfather and the mother of these siblings became ataxic at about 49 and 39 years respectively. Transmission was thus through both the male and the female line. While the pathological changes are quite consistent with the diagnosis of parenchymatous cortical cerebellar atrophy, these cases should, perhaps, be regarded with some reserve because of the fact that all of them died within one or two years after the onset of neurological signs. All were complicated by rapidly progressive severe dementia. In the series of Hall, Noad and Latham (1941) there were 9 afflicted members of two consecutive generations. In the first generation there were 2 females and 2 males who showed the disease; 1 male who died at 40 did not. The females of this generation left no offspring. One of the affected males transmitted the disease to 2 of his daughters, the other to 2 daughters and 1 son. The children of the unaffected male did not show symptoms. In the first generation symptoms appeared about the middle of the sixth decade, in the second generation during the fifth decade. The proportion of affected females to males in this family was 6:3. Neither of the parents of the first generation showed symptoms, the mother dying at 80, the father at 40. Transmission was through the male line in the two affected generations. In the family dealt with by Weber and Greenfield (1942) there were 4 affected members, all females, in 3 consecutive generations. Symptoms of unsteadiness of gait and slurred speech began at 60 in the first and second generation. In the third generation there were 9 offspring all of whom died in infancy except the two affected members, both of whom developed only moderate cerebellar signs at 40 years of age. The brain of the patient in the second generation was examined and has already been referred to, as have also the pathological findings in one of the cases of Hall, Noad and Latham's family. The example reported by van Bogaert (1947) and classified anatomically by him as parenchymatous cortical cerebellar atrophy ("atrophie cerebelleuse tardive du type Marie-Foix-Alajouanine") came from a family in which 5 members in 3 generations showed signs of pro-

gressive cerebellar disease beginning in the sixth or seventh decade. With them, gait disturbances and incoordination in use of the extremities were the outstanding signs, intention tremor and disorders of speech being absent. One female in the first generation had the disease and transmitted it to 1 daughter and 1 son. The latter in turn passed it to 2 of his sons. The female to male ratio was 2:3, and transmission was once through the female line, once through the male.

Thus the hereditary cases of Hull, Noad and Latham, Weber and Greenfield, of Akelaitis and of van Bogaert exhibited a dominant form of heredity. Bell and Carmichael (1939) in their analysis of all hereditary ataxias found that recessive inheritance was three times as frequent as was dominant, but that dominance became more frequent in those cases with late onset. It is probable that some of their late cases belonged to the group of primary cortical cerebellar atrophy, but the study included no pathological data on which to base a diagnosis. It should be pointed out also that a recessive mechanism is often extremely difficult to establish for man. One may easily fall into the error of assigning recessive qualities if one does not take into account the great variability of manifestation shown by many dominant genes. Such variablity includes the age of onset; so that a parent possessing the dominant gene may die before the hereditary character in question becomes apparent. The factor of mutation, too, may account for sporadic cases mistakenly classed as recessive and, finally, many human genetic histories are of necessity incomplete or misleading.

The pedigree of the family under consideration in this report offers some points worthy of comment. While the data do not permit a final explanation of the mode of inheritance of the disease, it would appear that in this family the mutant gene is dominant and produces its effects chiefly in the female sex. The fact that the disease appeared in two consecutive generations four times and in three consecutive generations once and that in five instances the disease was transmitted by an affected parent to its offspring indicates strongly that a dominant heredity was operative.

In three cases (*III*-J, *III*-C and *IV*-F), two of them sisters, the disease appeared in progeny of mothers who did not themselves show the disease (*II*-SA and *III*-A), but it is likely that they carried the dominant gene and failed to manifest signs of it because they died at ages (63 and 45 yr.) before they might have been expected to develop symptoms. That the minimum age of onset of the disease in this family is 60 years undoubtedly influences the pedigree in a number of ways. In calculating ratios and percentages of incidence in the several generations and sub-families one must consider not merely the total number of individuals, male and female, but primarily those who have lived to 60 years.

The great preponderance of affected females, 14:1, is the next striking feature. In generation *II*, where 88% of the females over 60 are affected, and no males, the explanation may lie in the fact that there were 10 females (8 over

60) and only 1 male among the siblings. In generation *III*, however, where there were 10 males and 12 females over 60, 50% of the females are affected, and none of the males, and in generation *IV*, 20% of the females over 60 and 10% of the males show the disease. In the whole of the three generations involved, 60% of females and only 5% of males over 60 are afflicted. The same trend is evident if one examines the subfamilies in which the disease appeared, as shown in table 1. It will be noted also that the total sex ratio of 29 females to 32 males is not abnormal. An analysis of all children over 60 years of age of

TABLE 1

CHILDREN OF:	●	○ >60	○ <60	○ ?	■	□ >60	□ <60	□ ?
II-H:	1	1	0	0	0	2	3	0
II-SA:	2	0	1	0	0	4	1	0
II-E:	1	4	2	0	0	0	2	0
II-L:	1	0	0	1	0	0	0	2
II-Lou:	1	0	0	2	0	1	0	0
II-R:	0	0	0	0	0	0	2	0
II-Car:	0	0	0	0	0	0	3	0
III-A:	1	0	0	3	0	0	0	1
III-C:	0	0	0	2	0	0	0	3
III-J:	0	0	0	0	0	1	0	0
III-M:	0	0	1	0	1	0	1	0
III-EL:	0	0	0	2	0	0	0	3
III-F:	0	0	0	3	0	0	0	2
	7	5	4	13	1	8	12	11

TABLE 2

	AFFECTED	NORMAL	TOTAL
Daughters	7	5	12
Sons	1	8	9
Total	8	13	21

affected or "carrier" mothers is given in table 2. Here again the preponderance of incidence in females is striking, with a ratio of affected to normal daughters of 7:5 as contrasted with 1:8 for the sons. When the exact probability for this 2×2 table is computed, the difference is seen to be statistically significant ($P = 0.037$). The very high percentages of females showing in some of the families is probably not entirely correct owing to the fact that the ages of all the unaffected females are not known and they are not therefore included in the group over 60. Nevertheless, that affected females far exceed affected males is unmistakable. This suggests that the dominant gene is probably more severe

in heterozygous females, producing an earlier average age of onset in females than in males.

It appears that the disease is transmitted without exception through the female line. This, however, may be more apparent than real, since in generations *II* and *III* there were 13 females, but only 4 males, who had offspring over 60, and from generation *II* there were 21 descendents over 60 from a female parent as against only 4 from a male.

A very striking decrease in incidence appears from generation to generation. In generation *II* 64% of all the individuals in it were affected; in generation *III*, 13%; and in generation *IV*, 3%. Such behavior would be expected of a dominant mutant giving a late average onset of symptoms. It is probably attributable, at least in large part, to the circumstance that the proportion of individuals over 60 years of age falls progressively as follows: generation *II*, 82%; generation *III*, 48%; and generation *IV*, 24%; or more particularly, a drop in the number of females over 60: generation *II*, 73%; generation *III*, 26%; and generation *IV*, 9%. In any event, this sort of attenuation of the activity of a dominant gene in a smaller and less well documented family might well account for the appearance of presumably "sporadic" cases.

An extraordinary longevity is a further characteristic of the family. The number of individuals in generations *II* and *III* who reached the ages of 70 to 100 is exceptional. This circumstance too undoubtedly has a bearing on the pattern of heredity exhibited by the disease. Had the life span been shorter or more nearly average, a gene with such a delayed incidence of effect as this one would have small chance of manifesting itself with the regularity seen in generations *I* and *II*. One would anticipate instead a more disconnected pattern, perhaps even "familial" or sporadic.

It should be pointed out that the above remarks apply only to this family. When the genealogies of all of the well verified instances of hereditary parenchymatous cortical cerebellar atrophy are considered, it is apparent that the only feature common to them all is dominance and that there is no uniformity as regards sex incidence or transmission.

It seems, then, that a case has been made for the essentially hereditary nature of parenchymatous cortical cerebellar atrophy. Whether there are also acquired forms of this clinical pathological entity must be left open. Certain cases of short duration and some in which mild awkwardness appeared after an infection or intoxication in early life, to be followed much later by a progressive and well marked cerebellar syndrome, suggest that there is such a group of extrinsic and varied etiology, though this has never been shown conclusively. Unless there is definite evidence to the contrary, it would seem proper to regard even the sporadic cases as hereditary. The situation is quite like that presented by olivo-ponto-cerebellar atrophy. The two are separate and distinct varieties of what Marie called, too simply, hereditary cerebellar ataxia. The less uniform

and well defined hereditary spino-cerebellar ataxia, exemplified by the classical cases of Sanger Brown, is perhaps another subdivision of the group. There may well be fundamental relationships between all three which crop out now and then as deviations from the standard formula toward features of the other types. The ophthalmoplegia in my Case 3, for example, is quite out of place in late cortical cerebellar atrophy and recalls the spino-cerebellar forms. Such atypical, inconstant variations and accessory manifestations are common to hereditary diseases of all organic systems, and need not confuse or obscure their recognition when the essential features are well marked as they are here.

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Breast Cancer in One Family Group[1]

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INTRODUCTION

THE possibility of an inherited tendency for breast cancer has been considered by a large number of capable investigators over a period of many years. Some students of the problem feel that multiple cases of cancer of the same type in certain families suggest an explanation based on heredity. Others insist that such concentrations of the disease can be explained by the phenomena of chance. The widespread distribution of breast cancer in the population makes difficult the selection of suitable control groups for comparison. Evidence from statistical data, family history analyses and studies of twins favoring an hereditary predisposition has been presented by Macklin (1940), Martynova (1937), Smithers (1948), Penrose *et al.* (1948), Jacobsen (1947), and Crabtree (1941). This evidence has been supplemented and analyzed critically by Habs (1938, 1938–39, 1939), Busk (1948), Karn (1948), Wassink (1935), and others. The problem is a difficult one and conclusive proof for or against any particular hereditary mechanism has not been obtained.

The critical study of one family group (Kindred 107 in the Laboratory of Human Genetics at the University of Utah) has provided data suggestive of an hereditary explanation. Breast cancer and breast tumors (some probably cancerous) have occurred much more frequently among the women in some branches of this kindred than in other branches, and more frequently than would be expected by chance in the general population. The members of different branches of this kindred have lived under the same general environmental conditions and, therefore, a direct comparison between those branches in which a high incidence of cancer has occurred and those in which little or no cancer has occurred seems valid. The individual members are shown diagrammatically in figures 1 and 2. The concentric rings represent generations and the individuals are numbered from right to left in order of birth in each sibship.

The data have been obtained through personal interviews with members of the families concerned. There are many technical, medical details with which lay people are not familiar. However, through careful questioning of different members of the same family it has been possible to obtain a fairly clear under-

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standing of the incidence of breast cancer and breast tumors in this family. Breast cancer is more conspicuous than most other types, and evidence obtained from the families has proved to be reliable. Verification has been obtained in most cases from doctor's records and death certificates. The information obtained from the families has checked remarkably well with that secured from the records.

Kindred 107 is one of ten kindreds selected for a preliminary study of the inheritance of cancer in Utah families. The objective of the pilot study was to try out the methods proposed for a larger project and determine whether or not reliable information can be obtained from the lay people concerned, and other sources available. Some of the ten kindreds were suggested by doctors who knew that certain types of cancer had occurred among members of the group. Others were selected from the sampling of death certificates. Some were chosen only because they were large kindreds and were believed to be representative of the population of Utah. Kindred 107 was first suggested by a student who used one branch of the family as the subject of a term paper for a course in Human Genetics. Another branch of the kindred was suggested by a doctor who had treated members of the group. Still another lead was obtained by the sampling of death certificates. It was not known at the time the study began that these three suggestions would lead to the same kindred. As the study progressed other independent leads were directed toward this family group.

Obviously this pedigree when presented alone reflects some degree of bias. However, the present phase of the project was not designed to approach the problem from a statistical standpoint. Another part of the study, now in progress, is directed toward that goal. In this larger phase it is proposed to analyze a large random sample of the present population of Utah. It is conceivable that all kindreds with progenitors going back three or four generations in the State will eventually be included in the study. The analysis of kindred 107 seemed to present an interesting case, worthy of continued observation. An experiment has been designed to follow members of this and other kindreds over a period of years for the purpose of securing precise clinical information concerning the family pattern and the onset of the disease in individual cases.

HISTORY OF THE MEMBERS OF KINDRED 107 AND INCIDENCE OF BREAST CANCER

Kindred 107 has descended from a man and his wife who emigrated from England to the United States in 1857. Their four oldest children (*II-1, 2, 3, 4,* figure 1) were born in England. The oldest daughter (*II-1*) was ten years old when the family came to the United States. No relatives of either the man or his wife have been located in America. Within two or three years after their arrival they took up land in a small valley at high elevation in the western part of the country and became the original settlers in what is now a small town in

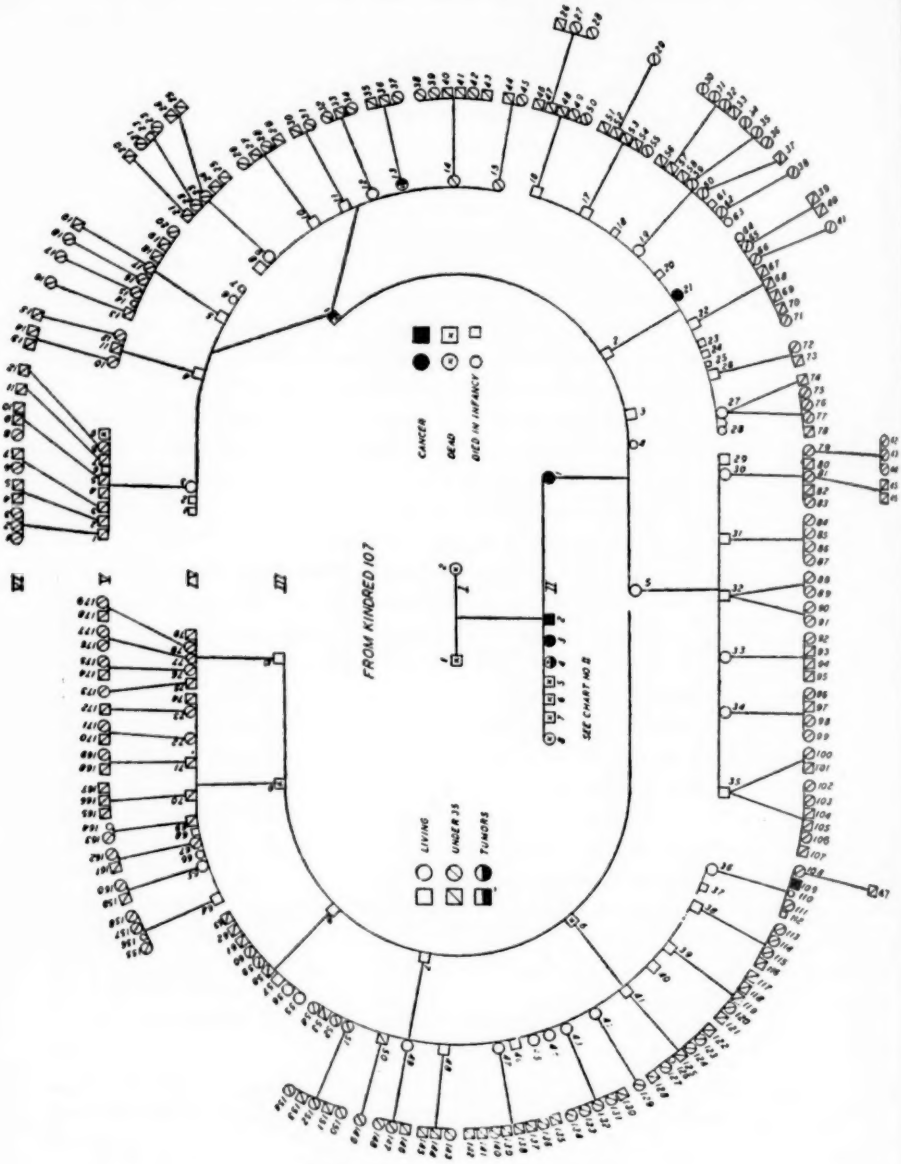

FIG. 1. Breast cancer in Kindred 107

the center of an extensive stock raising area. This became the family home. Four more children were born at this location. All eight children were nursed

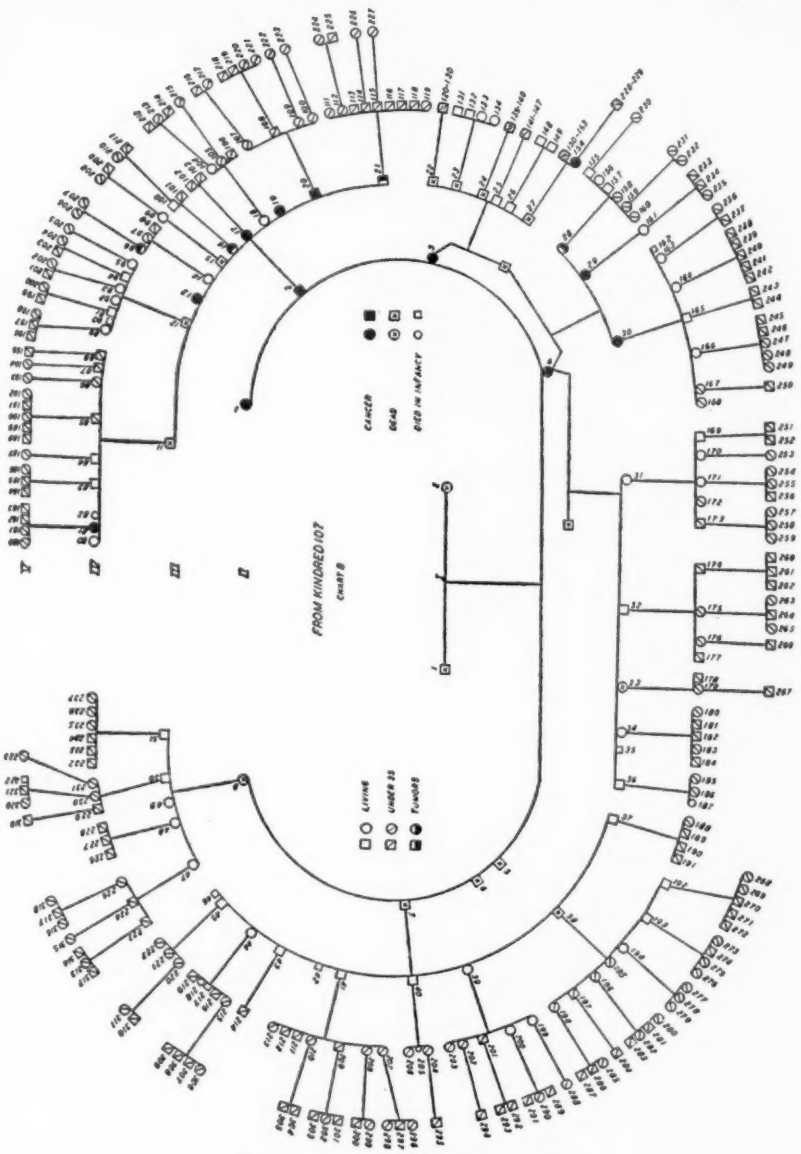

FIG. 2. Breast cancer in Kindred 107

by their mother. The man died at the age of 81 from causes incident to advanced age and his wife died at the age of 75 from unknown causes. The doctor indicated after her death that she may have had appendicitis.

Figures 1 and 2 represent all of the descendants of the original couple. The oldest daughter (*II-1*, figure 1) was married while a young girl and lived on a farm near the family home. She had ten children before she reached the age of 36. All ten children were breast-fed. Soon after her last child was born, she complained of painful lumps in her breasts. She became alarmed and went to a "salve" doctor for treatments. Later, after the condition was well advanced, she was treated by a medical doctor without success. She died at the age of 37 from breast cancer. Nine of her children, eight sons (*III-1*, *2*, *3*, *6*, *7*, *8*, *9*, *10*) and one daughter (*III-5*), reached maturity. The daughter is now 72 years old and in good health. Among the descendants of *II-1* two cases of cancer (*IV-21* and *V-109*) have been detected. These were not breast cancer and were of widely different types. *IV-21* died from abdominal carcinoma following an injury a year before. *V-109* died of lympho-sarcoma when only a young boy. Two cases of abdominal tumors (*III-1* and *IV-13*) were detected. The death of *IV-13* was probably caused by stomach cancer. The pathological records of this case are not available at the present time. It might be presumed on the basis of present evidence that the breast cancer expressed in *II-1* was not transmitted to any of her descendants.

The oldest son (*II-2*, figure 2) spent nearly his entire life in the community in which his parents had settled. He was a stockman and owner of a flour mill. He had three operations for cancer during the latter part of his life. The last of the three was performed to remove a cancer in the region of the navel, when he was 64 years of age. The cancer reappeared in the same location a few months after the operation. He died from a stroke in the latter part of the same year in which the operation was performed. His wife had grown up in the same community. She nursed all of her eleven children. At 75 years of age she died from causes incident to advanced age. Her six brothers and sisters had large families. The family group now numbering several hundred is well represented in the community and in the state. This kindred has been studied quite carefully. Only one case of cancer has been detected in the entire group. This case occurred in a niece of the wife of *II-2*. The diagnosis was carcinoma of the breast. The woman died of a heart attack following a radical resection of the breasts.

Among the eleven children of *II-2*, four daughters (*III-13*, *16*, *17* and *19*) have had breast cancer or presumably cancerous breast tumors. The tumors first appeared between the ages of 43 and 45 in all four women. *III-13* never married and spent many years as a sales lady in a department store. She had a breast operation at the age of 45 and died a year later from carcinoma of the breast. *III-16* married and became the mother of two children. She had a complete mammary resection at the age of 43. She is now 68 years old and healthy. *III-17* was a nurse when a young woman. She married and had two children. At the age of 44 she had a breast operation and died 15 months later with

"carcinoma of the breast, metastases general." *III-19* never married and worked as a secretary for a business firm. She had a breast operation at the age of 45 which was followed by radium treatment for carcinoma of the uterus. She died nine years later, following an operation for gall stones. One brother (*III-20*) of these four women died from carcinoma of the prostate with general metastases at the age of 59. Another brother (*III-21*) has had a chondroma removed from the rib and also a tumor removed from his jaw but no cancer has been detected.

The two other daughters (*III-14* and *III-18*) in the family of *II-2* are now in good health at the age of 72 and 64, respectively. Both have families of three children and both have nursed their children. The oldest daughter of *III-14* (*IV-96*) had a breast operation at the age of 32 and another 17 months later

TABLE 1. SUMMARY OF INDIVIDUALS IN KINDRED 107 (SYMBOLIZED IN FIGS. 1 AND 2)

Class	*Number*
35 years of age or over	127
Under 35 years of age	467
Tumors	7*
Cancer	13†
Died from other causes	18
Died in infancy	36
Total	668

* Includes 4 cases of breast tumors, three of which were probably cancerous. Three of the 7 individuals are living and four died from causes other then cancer.

† Includes 9 cases of breast cancer. Eight of the 9 individuals died from breast cancer and metastases. One died from other causes after the diagnosis of "carcinoma of the breast" had been made. All 13 individuals who have had cancer are dead.

on the other breast. Nearly 10 years have elapsed since the second operation and she is in good health. She had no children at the time of the operations but since has given birth to twin daughters. These daughters were fed from the bottle. The two younger children of *III-14* (*IV-97* and *IV-98*) are in good health. Among the male members of the family, the oldest son (*III-11*) died of kidney trouble at the age of 69. *III-12* died of unknown causes after a prolonged illness at 74, and *III-15* died in an accident at 26 years of age. The oldest son (*III-11*) had one daughter (*IV-81*) with breast cancer. She had a breast operation at the age of 33 and died with carcinoma of the breast one year later. The other seven children who reached maturity are in good health at the present time. Their ages range from 30 to 50 years. The children of *III-12*, *16*, *17*, *18*, *20* and *21* are all healthy at the present time. All are younger than 50 years of age.

The third child (*II-3*) of the original couple died at the age of 74 from carci-

noma of the lung which originated in the breast and axilla. She had six sons (*III-22–27*), four of whom have died from causes other than cancer and two are still living. One grand daughter of *II-3* (*IV-154*) died from carcinoma of the breast at the age of 42. *II-3* and her younger sister (*II-4*) both married the same man in polygamy. *II-4* had tumors in her breasts which caused her and her family a good deal of concern but the tumors apparently never metastasized. She married again after her first husband died and had a second family. She died at the age of 62 from pneumonia. In the first family of *II-4*, two daughters (*III-29* and *30*) died with carcinoma of the breast when they were about 40 years of age. Their oldest sister (*III-28*) had tumors in her breasts. She died from asthma and heart trouble at the age of 47 but evidence is available to indicate that she also had breast cancer at the time of her death. The descendants from the second family of *II-4* have been studied extensively but no cancer has been detected. Likewise no cancer has been found among the descendants of *II-7* and *8*. Most of these people are still under 35 years of age. The individuals in the entire kindred are classified in table 1.

DISCUSSION

Nine cases of breast cancer have been definitely established in the kindred here reported. In addition, four cases of breast tumors, three of which were probably cancerous, have been identified. Two of the four women in this latter group had the tumors removed by radical resection and are now living. The other two died from other causes and it is not known definitely whether or not the tumors were malignant at the time of their death. The evidence indicates that one had breast cancer at the time of her death. In the other case the tumors apparently never became malignant. The cases of breast cancer and breast tumors were distributed mainly in two branches of the family. This is consistent with the principles of Mendelian heredity based on particulate inheritance. No breast cancer nor breast tumors have been found among the descendants of the two younger members of the family. The women in this family who have had breast cancer have lived in widely separated parts of the United States and Canada. As far as it can be determined, those who have suffered from the disease and those who have not have eaten the same kind of food and worn the same type of clothing. No environmental factors have been suggested to account for the difference in the incidence of breast cancer in different branches of the family.

The age of onset and the history of the disease among members of the same family are surprisingly parallel. The tumors first appeared in all four cases in the family of *II-2* when the women were between 43 and 45 years of age. The duration of the disease and clinical history of the two women whose death was caused directly by breast cancer were parallel. Three sisters in the family of *II-3* also had breast cancer or breast tumors when they were in their forties.

Two died of breast cancer and very likely the third had breast cancer at the time of her death but she died from other causes. The similarity among these cases, involving members of the same family, suggests an hereditary mechanism.

The death rate from cancer in Utah over a period of years has increased but during the past few years has remained fairly constant. About 1 in every 103 deaths of all ages in Utah in 1946 resulted from breast cancer (Utah State Department of Public Health Morbidity and Mortality Report, 1946). In the family group under consideration 8 out of a total of 71, or about 1 in 9, deaths have resulted directly from breast cancer. Among those over 30 years of age, one death in about 80 was caused by breast cancer in the general population of Utah in 1946. In the same age group in kindred 107, one death in about four was caused by breast cancer over a period of years. Therefore, death from breast cancer among those over 30 occurred about twenty times more frequently over a period of years in kindred 107 than in the general population of Utah in 1946. All cases in kindred 107 occurred in members of the female sex. A more appropriate comparison could be made if only those of the female sex who reached maturity were considered. Unfortunately the statistics are not available to compute the exact ratio of female deaths past 30 in the two groups. If we assume that half of the deaths in that age group in the Utah population were among the females we should expect that one in about 40 females died from breast cancer in 1946. In the pedigree here considered, eight (*II-1*, *II-3*, *III-13*, *III-17*, *III-29*, *III-30*, *IV-81* and *IV-154*) of the sixteen females who died after reaching 30 years of age died from breast cancer and eight died from other causes. One (*III-19*) of the latter eight had breast cancer; another (*III-28*) probably had it; one (*IV-21*) died with abdominal cancer and another (*IV-13*) probably died with cancer of the digestive tract. One (*II-4*) had breast tumors at the time of her death. Among the other three, two (*I-2* and *III-33*) died from unknown causes. The other (*II-8*) died with typhoid fever. The probability of this concentration of breast cancer occurring by chance in one kindred is extremely low.

Evidence has been obtained recently by Graff *et al.* (1949) to indicate that the incidence of mammary tumors in cancerous strains of mice can be influenced by breast feeding or artificially feeding the new born mice. The possibility of a milk factor in human beings stimulates much interest. The present pedigree has provided no definite evidence for or against this possibility, but it is likely that evidence will be obtained as the study progresses. The oldest woman in the second generation (*II-1*) is reported to have nursed all of her ten children. She died with breast cancer when her youngest child was two years old. None of her descendants have had breast cancer but most of them are under 35 years of age. Only one of her daughters reached maturity. She is now 72 years old and in good health. The two younger sisters of *II-1*, (*II-3* and *II-4*) and the wife of her brother (*II-2*) all are reported to have nursed their children. In

the next generation all of the women are reported to have nursed their chldren The daughter of *III-14* (*IV-96*) had her breasts removed before her children were born and the children were fed artificially.

Since it seems likely that the problem of the inheritance of breast cancer will not be solved on the basis of information now available, a part of this study has been projected into the future. If there is an inherited predisposition involved, a given type of cancer might be expected to follow a definite pattern within a given family, suggestive of a genetic mechanism. Hypotheses to be tested have therefore been set up for family groups within kindred 107 as well as in other kindreds. These are based on the theory that heredity plays a part in the incidence of breast cancer.

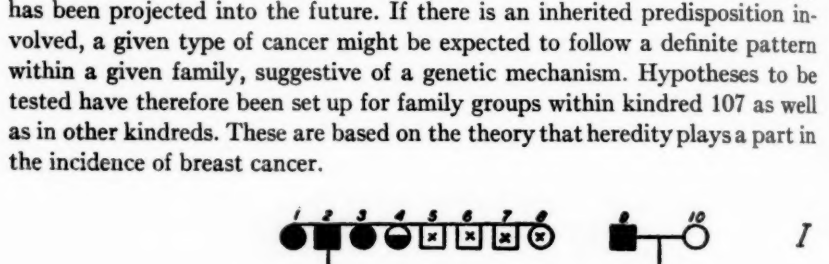

FIG. 3. Selected portion of Kindred 107, showing high incidence of cancer

To illustrate this plan an example is presented in figure 3. On the left at the top is shown the immediate family of the original couple from kindred 107. The children of *II-2* (fig. 2) are given and the children and grandchildren of *III-20* (fig. 2) are also represented. On the right is given the family into which *III-20* married. It will be observed from the pedigree chart (fig. 3) that the wife of *III-20* died from cancer. She died at the age of 58. The cause of her death was given as metastatic carcinoma of the brain due to carcinoma of the left breast with recurrence in the chest. Her sister (the only other member of the family) had both breasts removed by radical resection when she was in her forties. The father of these women had cancer of the prostate. Their mother is now living at the age of 86. If breast cancer is inherited the children and grandchildren of *II-10* and *II-12* (fig. 3) are in a vulnerable position. To determine whether or not breast cancer continues to occur with the expected

frequency in the next generation, it is proposed to test the hypothesis for the inheritance of the disease by continued observation of these individuals and others in similar family groups with a history of breast cancer. Clinical and laboratory facilities are being made available for the detection work. Appropriate examinations will be provided for women in selected family groups every four months.

An additional objective of this part of the project is to detect conditions which may precede breast cancer, if possible, and thus provide data for another phase of the complex cancer problem. Such examinations for selected groups should also have great practical value in providing early diagnosis for the people concerned.

SUMMARY

One Utah kindred including 668 individuals has been used as the basis for a study of the inheritance of breast cancer. Nine cases of breast cancer and four cases of breast tumors have been identified. The frequency in this kindred is about twenty times as great as that in the general population in Utah over the age of 30. One in about 40 females who died in Utah in 1946 died with breast cancer. In this pedigree one half of the deaths of mature females resulted from breast cancer directly. Some of those who died from other causes had breast cancer or breast tumors at the time of death. Most cases are concentrated in certain branches of the kindred while none have been detected in other branches. The period of onset, duration of the disease and general clinical history are remarkably similar among members of the same families. The data indicate that heredity is a predisposing factor for breast cancer, but the nature of the inheritance is not known. To investigate this further and, if possible, to discover the nature of the hereditary mechanism involved, tentative predictions have been made on the basis of these data for the future with reference to the incidence of breast cancer in certain selected groups. Members of these groups will be given regular physical examinations to detect the presence of cancer or precancerous conditions as early as possible.

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Cancer of the Lower Digestive Tract in One Family Group[1]

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INTRODUCTION

NINE cases of carcinoma of the lower digestive tract have been detected among the descendents of one couple. A total of 45 members are included in the group. The primary site in eight of these cases was localized in the bowel or rectum. Both sides of the family have been traced as far as possible. No cancer has been detected in the father's side. The mother died with cancer of the bowel. One of her brothers likely had cancer of the digestive tract but died in an accident. Another brother had cancer of the lip. A half sister had tumors (probably cancerous) removed from her breasts. Four of her more distant relatives died from cancer of the digestive tract. One relative has had rectal tumors removed, one has had breast tumors removed and another has had abdominal tumors removed. The evidence indicates an inherited tendency favoring carcinoma of the lower digestive tract coming through the mother's side of the family.

The data have been obtained from personal interviews with members of the immediate family concerned and members of other related families. The neighbors and close associates were also interviewed. The information obtained from these interviews was verified as far as possible from medical records and death certificates. Detailed clinical information concerning some of the more recent cases has been obtained from the doctors who have treated and who are now treating the members of the group. Unfortunately most of those who have had the symptoms are dead and several of the doctors are no longer available. Arrangements are now in progress to provide complete medical examinations for all members of this family group now living, along with the members of other families having a history of cancer of the lower digestive tract. The objective of this examination project is twofold: to secure further information for the genetic analysis of cancer of the lower digestive tract and to provide early diagnosis for polyposis and precancerous conditions for the good of the people concerned. One case of polyposis has recently been detected in this group by a private physician and will undergo surgery in the very near future. Throughout the study attention is being given to the advisability of early diagnosis and careful clinical follow-up of relatives of patients with proven cancer of the lower digestive tract.

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This family group is a part of one of twenty-five kindreds now being investigated for the incidence of cancer. Some of the kindreds in the larger study were suggested by doctors, some were selected from the sampling of death certificates and some were chosen because they are large kindreds well represented in Utah and readily available for study. This particular one (Kindred 109) was first suggested by a medical student who was interested in the possible inheritance of cancer in a family which had come to his attention. Another lead to the same group came from the sampling of death certificates. Several other families showing a history of polyposis and cancer of the lower digestive tract are included in the larger study. The pedigree reported here is the most extreme case encountered so far, but a comparable pattern is observed in other kindreds, suggesting a simple dominant mechanism of inheritance. The data available for the different members of the family group with the source of these data are given below. Since the methods of diagnosis and treatment for cancer of the lower digestive tract have changed considerably in recent years the dates are given with the case histories to facilitate proper orientation.

HISTORY OF THE FAMILY GROUP AND INCIDENCE OF CANCER

The members of the entire kindred (Kindred 109 in the Laboratory of Human Genetics, University of Utah) are shown diagrammatically in figures 1 and 2. The concentric rings represent generations and the individuals are numbered from right to left in order of birth in each sibship. The kindred has descended from one man and his two wives. The four children (*II-1* to *4*) of the first wife and their descendants are symbolized in figure 1. The eight children (*II-5* to *12*) of the second wife and their descendants are represented in the right hand side of figure 2 (family *A*). The only daughter (*II-7*)[2] of the second wife, died in 1909, at the age of 53. The death certificate lists the cause of her death as "cancer of the bowel." The doctor who treated her is not available. The nurse who cared for her is now past 80 years of age but seems mentally alert. She describes clearly and consistently the symptoms and prolonged suffering of *II-7*. The description fits well a case of cancer of the bowel. The relatives and neighbors who were present at the home of the patient during the period of her illness and death tell a similar story. Although no pathological examination was made and no medical records are available the evidence favoring "cancer of the bowel" as stated in the death certificate is convincing. Her husband (*II-15*) was killed in an accident at the age of 34. His three brothers (*II-13, 14, 16*) died at the ages of 95, 77, and 80 respectively from causes incident to advanced age. *II-13* and *II-16* had no children. *II-14* had nine sons and daughters (*III-71* to *79*) who now have a number of descendents (*III-227* to *259*). No cancer has been detected in this family (family *B*, figure 2). No other relatives of *II-15* have been located.

All four of the children of *II-7* and *II-15* very likely had cancer of the bowel or rectum at the time of their death. *III-67* had an operation on the lower digestive tract in 1934 at the age of 57 and died eight months later, at the age of 58. According to the death certificate he died with "carcinoma of the rectum." An intimate friend with whom *III-67* had lived and worked most of his life took care of him during his illness. The friend describes graphically the symptoms and intense suffering of *III-67* before and after the operation. He tells of

[2] *II-7* and *II-15* have been moved away from their proper places in their respective families for convenience in making the chart.

going to the nearby pasture and cutting sections of moist sod with a shovel and bringing it into the house to use for cold packs on the abdomen of *III-67* to relieve the pain. Relatives who were present in the home tell the same story. There is a striking similarity between the symptoms experienced by *III-67* and his mother *II-7*. The evidence strongly supports the cause of death as recorded on the death certificate. *III-68* died in 1921 at the age of 41. "Carcinoma of the bowel" was the cause of death according to the death certificate.

III-69 was living in a different community at some distance from the family home at the time of her illness and death. She died in 1916 at the age of 33. The death certificate lists "carcinoma of the rectum" as the cause of death. She was treated by a doctor not acquainted with other members of the family. The case history strongly supports the cause of death listed on the death certificate. *III-70* was living in another state at the time of his illness and death. He had an operation for carcinoma of the lower digestive tract in 1942 at the age of 56 and died a few months after the operation. The cause of death was reported as accidental, but the letters received by other members of the family, immediately preceeding his death, and the conditions surrounding his death, indicate that he took his own life. He wrote his niece (*IV-214*) to the effect that the "curse of the family" had returned, following the operation. He told other family members that he had cancer like his sister and brothers who were dead. His wife was dead and he was very much discouraged.

In the next generation, four have died with cancer of the digestive tract. They were living in widely separated areas at the time of their illness and death. Three of these cases (*IV-208*, *215*, and *216*) were described in the death certificates as "carcinoma of the rectum" and one (*IV-222*) was described, following the autopsy, as "adenocarcinoma of the stomach and metastases." *IV-208* had an operation on the lower digestive tract on February 5, 1937 and died on February 12 of the same year with "carcinoma of the rectum." She was 34 years old at the time of her death. Her infant son (*V-162*) died on May 9, 1936 at the age of two months. The cause of death was reported by the attending physician on the death certificate as "pyloric stenosis and peritonitis." *IV-208* was ill with cancer at the time the child was born. Her daughter (*V-163*) is now 18 years of age and apparently in good health. The eldest living member of this family group (*IV-209*) is now 44 years old. At present, he has two large tumors on the jaw and face. He is a farmer who works hard and is apparently in good health. He has not yet had an examination of the lower digestive tract. *IV-210* died at the age of 22. The cause of his death was listed in the death certificate as "intestinal flu." *IV-211* is now living. He has not yet been examined. *IV-212* was killed in an accident when 11 years old and *IV-213* died with cerebrospinal meningitis when only one month old.

In the family of *III-68*, two sons (*IV-215* and *216*) both died, according to the death certificates, with "carcinoma of the rectum." *IV-215* died in 1940 at the age of 35 following an earlier operation. He had trouble with his digestive system for several years preceeding his death. In his earlier life he had surface tumors removed from his forehead and back. His oldest daughter (*V-168*) now 19 years old has had a lump removed from her head and another still remains. His son (*V-170*) now 12 years old has surface lumps on his body. In a superficial examination one of the writers observed seven lumps, six in the head, neck and back region and one on the lower arm, ranging from the size of a quarter to that of a small hen's egg. These are subcutaneous swellings which are likely not related to the cancer of the lower digestive tract. This group will be given a careful examination in the near future.

IV-216 died on July 31, 1936 at the age of 29 from "recurrent carcinoma of the rectum," following an operation on the lower digestive tract performed on December 20, 1935. He had a tumor removed from his jaw about six months before the operation on the lower digestive tract. *IV-219* has had a surface tumor removed from his back. A recent illness brought him to his family doctor who discovered a condition of polyposis in the colon. He

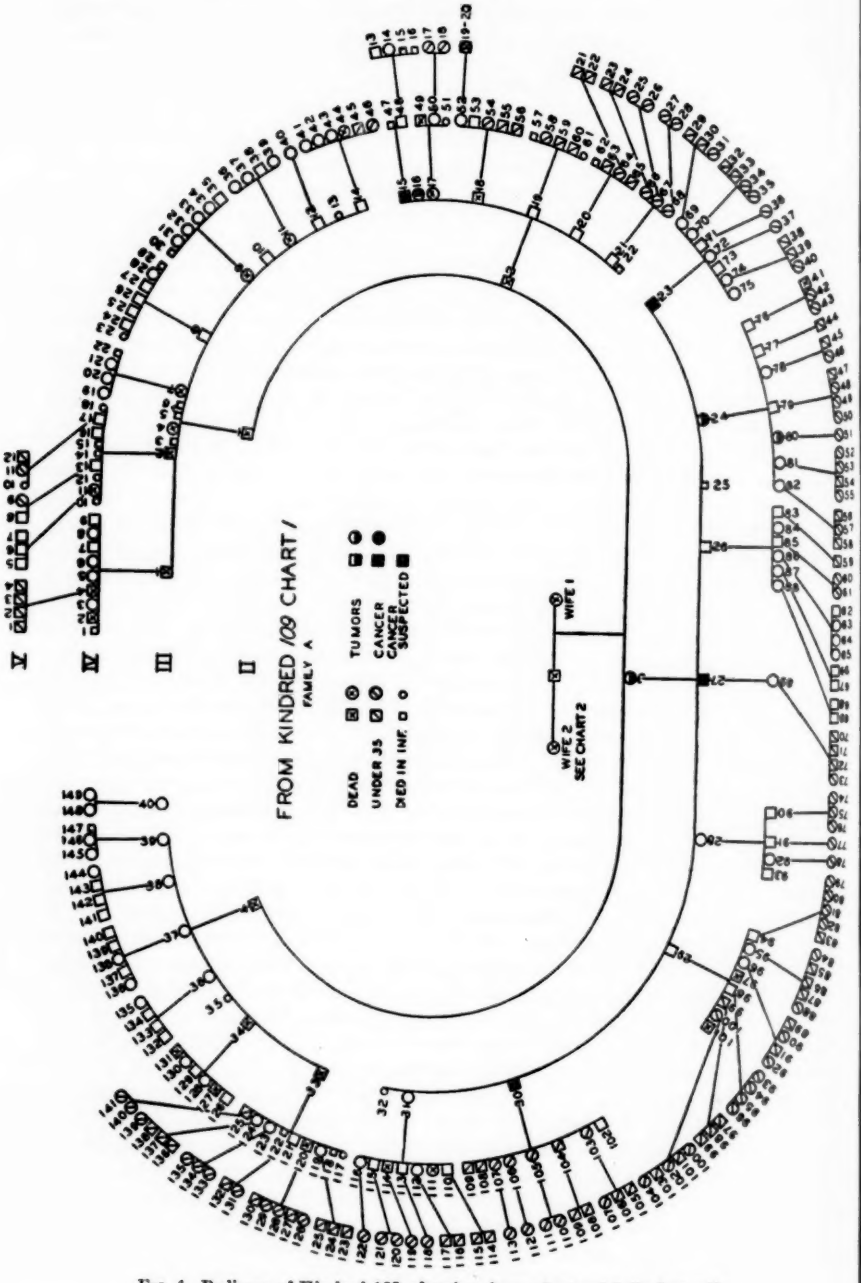

FIG. 1. Pedigree of Kindred 109, showing descendents of *I-2*'s first wife.

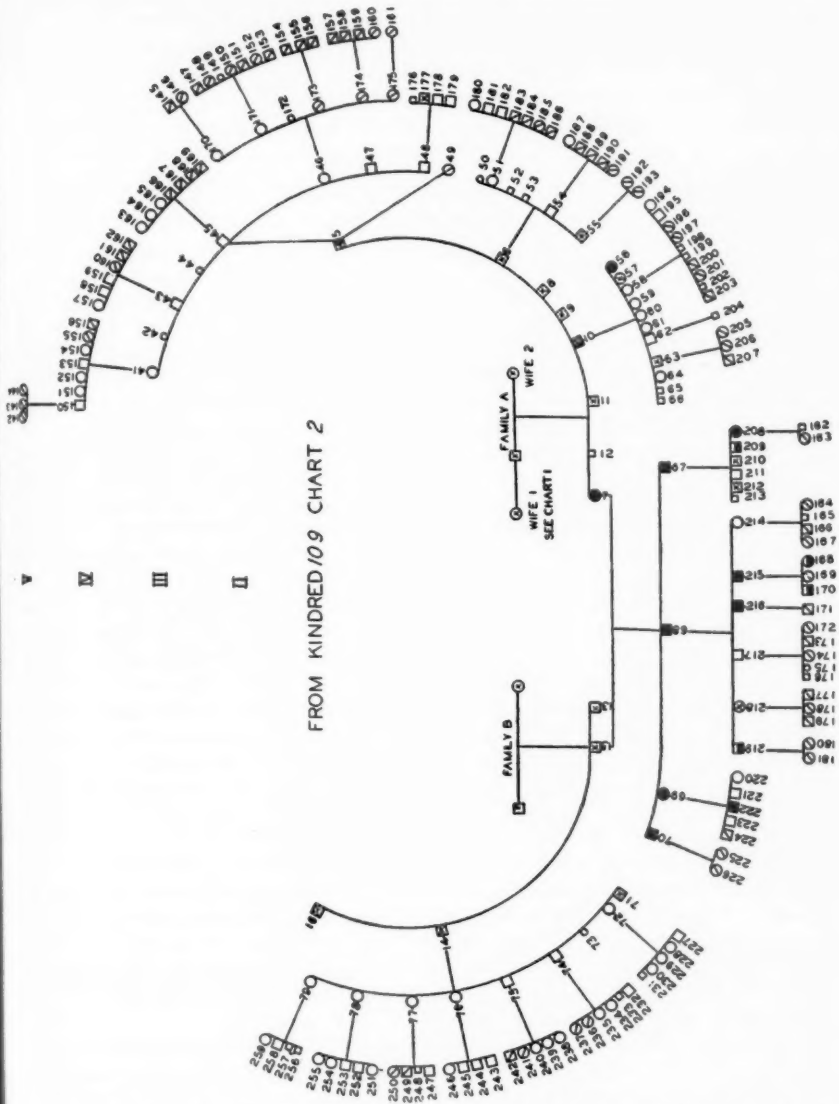

FIG. 2. Pedigree of Kindred 109, showing descendents of *I-2*'s second wife and Family "B", connected by marriage to Kindred 109.

has been referred to a surgeon and will undergo surgery in the very near future. He is now 35 years of age. *IV-218* was killed in an accident at the age of 29. The other two members of the family (*IV-214* and *217*) are apparently in good health. All of the grandchildren of *III-68* are under 35 years of age. One son of *III-69* (*IV-222*) died in 1941 at the age of 31

with adenocarcinoma of the stomach with extensive metastases in different parts of the body including the region of the lower digestive tract. The cause of death was confirmed by autopsy. All of the other children of *III-69* are under 45 years of age. The youngest is less than 35. The two children of *III-70* are also under 35.

Among the descendents of *II-7* and *II-15*, 5 died in infancy, 8 are now over 35 years of age and 19 are under 35 years of age. Nine members of the family have died with cancer of the digestive tract and only four have died from causes other than cancer. Three of these deaths were accidental and one was attributed to intestinal flu.

Evidence for Polyposis and Cancer Among the Relatives of II-7

In the family (family *A*, figure 2) of the mother (*II-7*) of the family group described above several cases have been detected and others are suspected. Her brother (*II-10*, figure 2) died in an accident at the age of 70. He was ill at the time of his death and cancer of the digestive tract was strongly suspected but not confirmed. His oldest daughter (*III-56*) died in 1945 following an operation for carcinoma of the lower digestive tract at the age of 54. Generalized metastases were observed in the operation. She had undergone an operation for "carcinoma of the breast" ten years earlier. The oldest full brother (*II-5*) of *II-7* had cancer of the lip. Her half sister (*II-3*, chart I) had tumors (probably cancerous) removed from her breasts in 1921. She was in poor health for several years before her death. Cancer of the digestive tract was suspected by her relatives but she did not submit to surgical exploration. She died in 1931 at 77 years of age. The cause of death was listed on the death certificate as "apoplexy."

Among the more distant relatives of *II-7*, *III-15* had an operation a few months ago (1949) for cancer of the lower digestive tract. He is living but not well. *III-16* had a cancer removed from her face several years ago and has recovered. *III-23* had an operation on the digestive tract at the age of 63 and died following the operation. The cause of death as listed on the death certificate was "carcinoma of the stomach." *III-24* had a radical resection for breast tumors in middle life. She died in 1942 at 70 years of age. According to the death certificate the cause of death was "cirrhosis of the liver." *III-27* had trouble with his digestive tract for several years before his death. According to the death certificate he died in 1943 from "carcinoma of the stomach" at the age of 65. *III-30* died in 1937 at the age of 51 from "carcinoma of the stomach" following a gastric resection. *IV-80* had rectal tumors removed at the age of 50 and *IV-82* has recently had rectal tumors removed. In the entire kindred (109 or figure 1 and family *A*, figure 2) 49 died in infancy, 195 are now over 35 years of age, 14 have had cancer of the digestive tract and 39 have died from causes other than cancer. About 26 percent of those who have died after reaching maturity, in the entire kindred, have had cancer of the digestive tract. The evidence suggests that the predisposing factor (polyposis) for the cancer of the lower digestive tract is inherited and may have come to the family under discussion through the line of the mother (*II-7*).

No evidence of cancer of the lower digestive tract or polyposis has been detected in the families of *II-1*, *II-4*, *II-5* or *II-6*. Evidence suggesting the presence of this character has been indicated in the families of *II-2*, *II-3*, *II-7* and *II-10*. Three (*II-3*, *II-7* and *II-10*) of these latter four individuals very likely had the condition themselves. *II-2* died at the age of 60 with organic heart disease and it is not known whether or not he had polyposis at the time of his death. These data are in keeping with Mendelian principles of heredity and can be explained on the basis of a simple dominant mechanism of inheritance. The families of both wives of the original man show some expression of the trait.

DISCUSSION

Nine members of one family have died with cancer of the digestive tract. In eight of these nine cases the primary site has been localized in the bowel or rectum. Six were definitely established in the rectum and two were described more generally in the bowel. Only four members of the family who reached maturity have died from causes other than cancer. Three of these met accidental deaths at an early age. The incidence of cancer, and particularly cancer of the lower digestive tract, is much greater in this family than that of the general population of the state (Utah State Department of Public Health Morbidity and Mortality Report, 1946). In Utah, the death rate from cancer of all types was 79.37, 79.68, 83.92, 76.30, and 76.30 per 100,000 population for the five years from 1942 to 1946, respectively. In the family group under discussion, nine of a total of 45 members have died with cancer. The death rate calculated from these figures would be 20,000 per 100,000. Only about 4 percent of the cancer deaths in Utah in 1946 were attributed to cancer of the rectum. Six of the nine, or about 66 percent of the cancer deaths among members of this family were established as cancer of the rectum. Figures are not available to compare the cases localized in the colon, with the general population of Utah. However, all nine of these cases were localized in the digestive tract and the case histories have a good deal in common.

Obviously, this family group does not represent a random sample of the population of Utah. The comparison with the incidence of cancer of this type in the population is given merely to indicate the degree of concentration of cancer of the lower digestive tract in one family group. On the basis of this single pedigree, a simple dominant mode of inheritance is postulated for the predisposing factor (polyposis) involved. If this hypothesis is correct half of the children of a parent showing the trait would be expected to inherit the gene and, if penetrance is complete, express the character. No expression would be expected in families where neither parent carried the gene. Whether the family was picked at random or selected, this pattern would be expected to follow, if the hypothesis is correct. The objective of the study is to test the hypothesis by following this family and others showing a history of cancer of the lower digestive tract with careful and accurate clinical data.

The results of a study made by Jüngling and cited by Habs (1938–39) indicate that polyposis of the large intestine in which frequently a carcinoma develops is inherited as a simple dominant trait. Macklin (1932) has cited several cases of rectal polyps associated with carcinoma in family groups. Wassink (1935) has made extensive statistical studies of the families of cancer patients and has found that among the relatives of persons affected by cancer of the rectum and of the stomach, the mortality from cancer is considerably

higher than that of the average population. Several Members of the family described here have had tumors in various parts of the body including the lower digestive tract. Some who are now living and apparently in good health have tumors. These people will be provided regular medical examinations as a diagnostic measure for the benefit of the family concerned and as a means of obtaining more complete and reliable data concerning the onset of cancer, relationship between tumors and cancer, as well as the hereditary pattern in the family.

No environmental factor has been suggested to account for the high incidence of cancer of the lower digestive tract in this family. The family home is in a farming community and most of the older members of the family have lived all of their lives in the same community. Several people now living in the community have associated intimately, lived and worked, with the members of this family who have since died with cancer. No cases of the same type of cancer have been known to occur among other people of the community. Several of the younger members of the family left the family home while young and some of these, while living in widely separated parts of the United States, have died with cancer of the rectum. This suggests that an hereditary mechanism is a primary factor in the predisposition for this type of cancer.

SUMMARY

Nine cases of cancer of the digestive tract have been identified in one family group made up of a total of 45 individuals. The primary site for eight of the nine cases was established in the region of the bowel and rectum. Among those who have reached maturity, nine members of the family have died with cancer of the digestive tract and four members have died from causes other than cancer. No cancer has been detected on the father's side of the family. About 26 percent of the entire kindred from which the mother has come, who died after having reached maturity, have had cancer of the digestive tract. A simple dominant inheritance is suggested as a hypothesis to explain the inheritance of the predisposing factor (polyposis) for cancer of the lower digestive tract in this family. It is proposed to test this hypothesis by providing regular medical examinations for the younger members of the family and the members of other related families over a period of years.

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Gaucher's Disease: Cases in Five Related Negro Sibships

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GAUCHER'S DISEASE is a relatively uncommon disorder of lipid metabolism characterized by the accumulation of the cerebroside kerasin in the cells of the reticulo-endothelial system. The resulting hyperplasia leads to enlargement of the spleen, liver, bone marrow and lymph nodes. As kerasin cannot be demonstrated in normal blood or in the blood of patients with Gaucher's disease, Thannhauser *et al.* (1939) have suggested that the disease represents an intracellular metabolic defect rather than a storage disease.

The condition is widely distributed in Europe and North America, and has been described in India (Spackman & Mackie, 1925) and Japan (Reiss & Kato, 1932). Several cases have been described in Negroes, and many authors state that the condition is especially prevalent in the Jewish race. The age of onset may vary considerably. In the series of 89 cases tabulated by Hoffman and Makler (1929), 43% occurred in patients under 12 years of age, and 17% began under 1 year of age. The onset has been reported as early as 1 week of age (Siegmund, 1921), and DeLange (1940) and Köhne (1939) described cases beginning in infancy as a special malignant form with brain changes, and suggest that the infantile type should be considered a distinct clinical entity. At the other extreme, Bessie (1937) reports a patient first diagnosed at age 62 years, and states that the spleen was not palpable 7 months earlier.

The clinical course of Gaucher's disease is also subject to variation. Usually the onset is insidious with enlargement of the spleen, which may eventually fill almost the entire abdomen and descend into the pelvis. Enlargement of the liver usually follows splenomegaly. Pigmentation, especially of the skin of the legs and face, may appear later. Pingueculae—wedge-shaped brownish thickenings of the conjunctiva at the corneoscleral junction bilaterally—are also a late sign. Anemia and leukopenia are common, and a tendency to hemorrhage and easy bruising is frequent. Bone pain, which may be either mild or acute and severe, may occur at any time. As acute bone symptoms may be associated with fever, such episodes early in the course of the disease may be confused with acute osteomyelitis. Death is usually by intercurrent infection. The diagnosis may be made with reasonable reliability on clinical grounds alone, but a

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certain diagnosis depends on the demonstration of the typical Gaucher cell in sections obtained from bone marrow, lymph node or other material. An extensive clinical and pathologic description of the disease is given by Thannhauser (1940).

It is the purpose of this report to describe a Negro family in which five cases of Gaucher's disease have occurred in five closely related sibships. Two of these cases have previously been reported by Pachman (1938), and extensive clinical, pathological and biochemical studies were described. A photograph of these same two patients was also published by Snyder (1941).

CASE REPORTS

Case A. Negro female, born 1926. Development was normal until age 5 years when it was noted that the abdomen was becoming progressively enlarged, although general health was good. At age 8 years she began to walk with a limp and some shortening of the right lower extremity was noted. She was admitted to Duke University Hospital, Durham, N. C., on July 7, 1936. The patient was generally emaciated and the abdomen was enormous, with great enlargement of the spleen and liver, and shortening of the right leg. The erythrocyte count was 3,500,000; hemoglobin 6.8 grams; leucocyte count 3,560; platelet count 310,000. X-rays showed decalcification of all bones and a pathologic fracture of the neck of the right femur. Extensive clinical studies of this patient were carried out by Pachman (1938), and photographs, x-rays, and biochemical studies may be found in his paper.

The patient remained in fairly good health for the next two years, but was seen at intervals with edema of the ankles and cramping pains in the legs. Analgesics and a few days of bed rest would relieve these symptoms. Episodes of spontaneous epistaxis were fairly frequent, and blood was present in the stools on several occasions.

On June 30, 1939 (age 13 years) she was seen in acute respiratory distress. The temperature was 104°F, pulse 140/min., and respiratory rate 60/min. Moist rales were heard over the entire chest and she was expectorating blood-tinged sputum. Digitalis and morphine were administered and she seemed to improve and was more comfortable. Several hours later the temperature had fallen to 99°F, pulse 100/min., and respiratory rate 35/min. The leucocyte count was 4,300 with 60% polymorphonuclear cells. Shortly thereafter another episode of acute pulmonary congestion occurred and the patient expired. A gushing hemorrhage from the mouth and nose immediately preceded death. An autopsy was performed and typical findings of Gaucher's disease were demonstrated. The liver and spleen were tremendously enlarged and occupied most of the abdominal cavity. The lungs were congested and there was almost complete consolidation of the right lung and partial consolidation of the left lung. The microscopic sections were characteristic of the disease.

Case B. Negro male, born February, 1929. This patient is a half-brother of Case A. Development was normal for the first two years. During the third year he began to have "spells" described as a drawing backward of the head, stiffening of the neck, and jerking of the extremities and body. A physician made a diagnosis of intestinal parasites, treatment was given, and unidentified worms were expelled. At this time it was noted that the abdomen was enlarged and the physician is said to have palpated a mass in the left upper quadrant. The abdomen continued to enlarge gradually, but the general health was rather good.

At age 7 years some transient edema of the ankles appeared, and shortly thereafter (July 7, 1936) he was admitted to Duke Hospital. Positive physical findings at this time

included generalized lymphadenopathy, slight yellowish thickenings of the conjunctiva at the corneoscleral margins of the right eye, recent conjunctival hemorrhage of the left eye, extremely protuberant abdomen, spleen enlarged with lower pole at symphysis pubis and notch at umbilicus, and liver enlarged to 9 cm. below costal margin. The erythrocyte count was 3,600,000; hemoglobin 7.2 gm.; leucocyte count 4,000, with a relative lymphocytosis; platelet count 192,000. Biopsy of an axillary lymph node revealed typical Gaucher cells. X-rays of the long bones showed diffuse calcification with small areas of destruction in the necks of both femurs. Studies on fat metabolism were carried out by Pachman (1938), and his paper includes an extensive clinical description, photographs, X-rays of long bones, and pathological and biochemical findings.

Two years later (September, 1939, age 10 years), the patient was found to be poorly nourished, with a height of 47 inches (119 cm.) and a weight of 64 pounds (29 Kg.). The abdomen was extremely protuberant and pendulous (see photograph, fig. 1). The head was smaller than average for this age. The wedge-shaped conjunctival thickenings had become larger and were bilateral. The chest was funnel-shaped, and there was respiratory embarrassment and upward displacement of the heart. The apex impulse was palpated in the 3rd and 4th interspaces 1 cm. lateral to the left mid-clavicular line; the right border of dullness extended 3 cm. lateral to the right sternal margin. The cardiac rhythm was regular and a soft systolic murmur was heard at the mitral area. The blood pressure was 96/74. The circumference of the abdomen at the level of the pelvic crest was 35½ inches. The spleen and liver were tremendously enlarged and the lymph nodes were generally palpable but not tender. The patient became progressively weaker and expired on February 1, 1940. An autopsy was performed, and typical findings of Gaucher's disease were demonstrated.

Case C. Negro male born August 15, 1936. Development was normal during the first year except that he is said to have had rickets at age 8 or 9 months. After the child began walking, it was noted by the parents that the abdomen was pendulous, but a physician was not consulted. After age 2 there were several spontaneous hemorrhages from the nose and mouth.

When examined at age 3 years (July 8, 1939), the patient was small for his age. His weight was 27 pounds, and the following measurements were recorded: height, 33 inches; head circumference, 19½ inches; chest circumference at nipple line, 20½ inches; abdominal circumference at pelvic crest, 24½ inches. There were no pingueculae and the chest was normal except for a soft systolic cardiac murmur. The spleen was easily palpable, smooth, firm and non-tender, and extended to the midline below the umbilicus. The liver was also enlarged and reached almost to the border of the spleen in the left upper quadrant and 4 cm. below the costal margin in the right flank (see photograph, fig. 1). The cervical, axillary and inguinal lymph nodes were enlarged but non-tender. The patient ran a progressive down-hill course and expired on January 8, 1940. An autopsy was performed, and the typical changes of Gaucher's disease were demonstrated.

Case D. Negro male born 1939. Enlargement of the abdomen was noted by the parents prior to the child's first birthday, and progressively increased. When examined at age 2 years (March 4, 1941) he was poorly developed for his age with little subcutaneous fat and a protuberant abdomen. The spleen was enlarged, extending to the midline, and the splenic notch was palpated just above the umbilicus. The liver was palpable 5 cm. below the costal margin. The patient subsequently had several episodes of epistaxis and the course was rapidly progressive. He expired at age 2 years on June 6, 1941 and autopsy revealed typical findings of Gaucher's disease.

FIG. 1. Gaucher's Disease: *left*, case B; *right*, case C. A normal cousin of the same age as case C is also shown to indicate the general retardation of growth in the affected children.

Case E. Negro male born November 28, 1944. This child also developed enlargement of the abdomen at about age 1 year. Later spontaneous hemorrhages from the nose and

mouth were frequent. The spleen, liver and lymph nodes were enlarged as in the earlier cases. He had frequent episodes of diarrhea. He apparently had an unusual appetite for gritty substances, and red clay is said to have been a favorite item of diet. He expired on April 10, 1948 (age 3¼ years), but an autopsy was not obtained.

DESCRIPTION OF PEDIGREE

The five patients described above were all closely related, their relationships being indicated in the pedigree (fig. 2). The two couples indicated in the first generation are the earliest ancestors concerning whom definite information is available. A daughter (*II-5*), age 87, of the first couple was interviewed, and also a daughter-in-law (*II-9*) of the second couple. The daughter-in-law claimed to be 100 years old, and on examination seemed to be of about this age. Both of these informants thought that there was some kinship between the two first generation couples, but were unable to furnish exact data. All that is known definitely is that these two couples lived on adjoining farms in Davidson County, North Carolina, before the Civil War. Most of their descendants remained in the same rural community, and intermarriage among these descendants was frequent.

As the result of these intermarriages, most of the individuals in the fourth and fifth generations are related, and many of the fourth generation married cousins. Over a period of about 10 years, five patients with Gaucher's disease were recognized in five sibships in the fifth generation. As may be seen from the pedigree, the parents of four of these patients were related, in each case being second cousins. Of these four cousin marriages, the parents of three of the affected children (cases A, B, and E) have the first couple in generation *I* as common ancestors. The fathers of these cases are also descended from the second couple of generation *I*. The parents of case D are second cousins with the second couple in generation *I* as common ancestors, but the father is also descended from the first couple. The parents of case C are not known to be kin, but the father is descended from the first couple and the mother from the second couple of generation *I*.

The relationships between the five patients are rather complex, and are most easily visualized by means of a path diagram of the kind more familiar to animal geneticists (fig. 3). Each possible pair of patients is related by at least six pedigree paths, while there are no less than 10 paths connecting cases B and E. Cases B and D, for example, are connected by 9 paths, being half first cousins, as well as full second cousins and full third cousins in three different ways. The degrees of kinship are more readily expressed as *coefficients of relationship* (Wright, 1922), and these are of some interest as the patients are actually more closely related than would appear at first sight. The coefficients of relationship (r) are listed in fig. 3. Thus, the closest relationship, between cases A and E, is nearer that of full sibs ($r = .50$) than that of half-

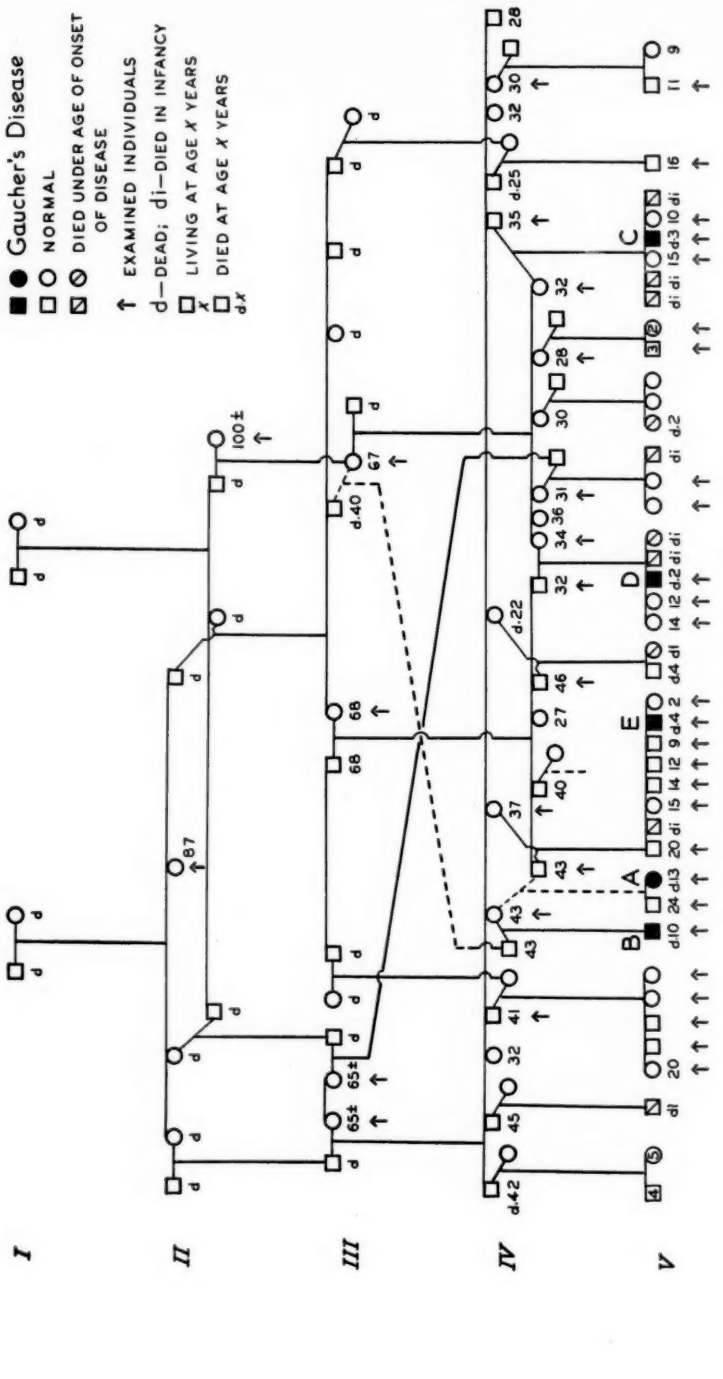

FIG. 2. Pedigree of five Negro patients with Gaucher's Disease

sibs ($r = .25$), while the most distant relationship is slightly less than that of full first cousins ($r = .125$). Also, it will be seen that all of the 10 relationships are *bilineal* in the sense defined by Cotterman (1941), i. e., between every pair of patients there are at least two paths which are completely independent, having no links in common. For example, the path connecting E and A through their father is independent of the paths connecting them through their mothers. Such relatives are commonly expected to both show a rare recessive trait.

In addition to the matings producing abnormal children, three other cousin marriages occurred among descendants of the two couples of the first generation and are indicated in figure 2. These three marriages gave rise to 6 children, of whom two died in infancy of unknown causes, one died at age 4 years of an un-

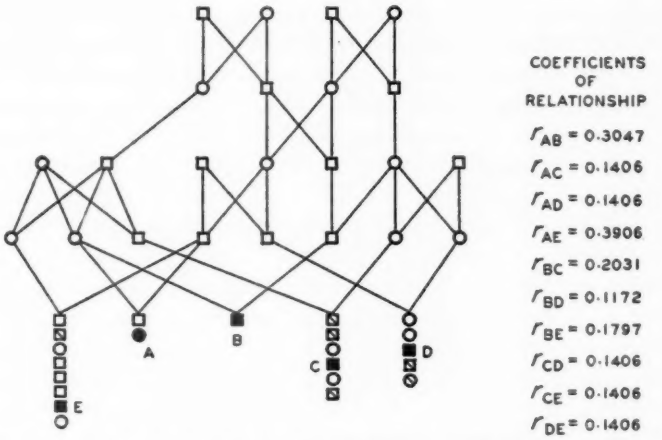

FIG. 3. Path diagram showing relationships between 5 cases of Gaucher's Disease

related disease, and three were examined and found healthy. To avoid undue complication of the pedigree, two additional cousin marriages that were without issue are not indicated on the diagram.

As the pedigree indicates, the five patients with Gaucher's disease collectively had 17 siblings, 10 male and 7 female. Of these, six (5 male, 1 female) died in infancy. Two of these died during the first 48 hours of life of unknown causes. Two died during their first summer of "colitis." The only female in this group died at age 3 months of bronchopneumonia. All of the mothers denied the occurrence of any stillborn infants or miscarriages. The youngest brother of case C died at age 6 months of bronchopneumonia, but the parents report that this child had an enlarged abdomen prior to the final acute illness, and the parents thought that he was developing the family affliction. This child was seen a few hours prior to death by a physician having no previous knowledge

of the family, and there are no records available bearing on the question of diagnosis of early Gaucher's disease. Of the eleven siblings of the patients who survived the first year of life, all were examined at ages ranging from 2 years to 24 years, and had no signs suggestive of the disease.

DISCUSSION

The genetic mechanism responsible for Gaucher's disease in this family may be deduced with reasonable reliability directly from the pedigree. The occurrence of multiple cousin marriages would be highly effective in bringing a rare recessive gene into homozygous condition. As is seen from figure 3, the 5 cases of Gaucher's disease collectively possess only 8 parents, 7 grandparents, not more than 12 great-grandparents, and not more than 20 great-great-grandparents. On the hypothesis of recessive inheritance, it is of course certain that all 8 parents were heterozygous for the gene, and that at least 3, but probably not more than 4, of the 7 grandparents carried it. The demonstrated relationships among the grandparents further allow us to assume that all defective genes in the pedigree may have been derived from one member of each of the two couples in generation *I*. Finally, on the basis of the alleged relationship of these two couples, it is possible that all 10 genes present in the 5 affected children in generation *V* may have descended from a single heterozygous ancestor shared by the two members of generation *I*. This is certainly a very likely possibility, although there are other possibilities which are perhaps not much less probable. Since the *coefficient of inbreeding* (Wright, 1922) for the 4 children arising from second cousin unions is only 1/64, it is probably not many times greater than the frequency of the recessive gene in the general population. Hence it seems not unlikely that at least one of the demonstrated inbreeding paths did not actually represent the path of descent, and that instead a second (independent) gene may be present. This second gene might be independent of the first in the sense of separate origin by mutation in a different ancestor. Or, it might be independent only from the point of view of the known pedigree. For example, a second gene, introduced through one of the 3 unrelated grandparents (generation *III*) might actually be of same descent as the first through relationship paths which are unknown. In either case, the multiple bilineal relationships among the patients offer innumerable opportunities for two such genes to explain the observed events.

If the children who died in infancy are removed from consideration, the ratio of normal to affected children in the affected sibships is 11:5, which is not significantly different from the expected ratio of 12:4. The total sex ratio of the affected sibships is normal, being 9 males to 7 females; even when the children dying in infancy are included, the sex ratio (14:8) cannot be regarded as a significant departure from the normal. Also, the deviation from expected

equal numbers of affected males and females is not significant, as a deviation from equality as great or greater than 4:1 would be expected in 3 out of 8 sibships of 5 by chance alone. The evidence supplied by the pedigree thus appears to be compatible in all respects with the hypothesis that Gaucher's disease is due to an autosomal recessive gene in the homozygous state.

The possibility that other genetic mechanisms might satisfy the conditions of this pedigree may be summarized briefly:

1. *Dominant.* The possibility that a dominant gene with reduced penetrance might account for the facts is extremely remote. With a ratio of normal to affected of 11:5 in the affected sibships, it would be assumed that the penetrance of the postulated gene must be at least 25 to 30 per cent, but all 8 parents and 7 grandparents of the affected individuals are normal, and no cases are known in earlier generations.

2. *Sex-linked Recessive.* This hypothesis could be satisfied only by assuming that heterozygous females occasionally show the disease, and that case A represents such an event. It would also be necessary to assume that the same rare gene entered the pedigree through two unrelated individuals, *II-9* and *III-2*. Furthermore, the ratio of normal to affected males among the offspring of known heterozygous females would be 12:4, a probably significant (chi-square = 4.0) deviation from the 1:1 ratio which would be expected on the hypothesis of a sex-linked gene.

3. *Partially Sex-linked Recessive.* The suggestion of an excess of males among the affected children raises the possibility of this mechanism, for, although partial sex-linkage is not expected to produce unequal numbers of affected males and females in a series of unrelated sibships, it would do so in a single large sibship, and indeed, the 5 sibships containing affected children in this kindred are so closely interrelated that they approach the equivalent of one large sibship.

An exact test for recessive partial sex-linkage would be very difficult, owing to the complexity of the pedigree. However, it may be shown that, even under a set of assumptions most favorable to the hypothesis, significant evidence for partial sex-linkage seems to be lacking. We assume first that the abnormal gene was introduced through 3, or possibly all 4, of the related grandparents, but not through any of the 3 remaining grandparents. Haldane's (1936) "direct method" for testing recessive partial sex-linkage can then be applied with some modification. Three of the patients, A, D, and E, have their fathers related to their mothers through their common paternal grandmother, but not (in any known way, at least) through their paternal grandfather. It may therefore be assumed that these three fathers received the abnormal gene (g) on their X-chromosome $(gx)(Gy)$. Denoting the cross-over frequency by χ, the probabilities and observed frequencies in the four classes of children are:

Children:	normal ♀♀	affected ♀♀	normal ♂♂	affected ♂♂
Probability:	$\frac{1}{4}(1 + \chi)$	$\frac{1}{4}(1 - \chi)$	$\frac{1}{4}(2 - \chi)$	$\frac{1}{4}\chi$
Observed:	$a = 4$	$b = 1$	$c = 5$	$d = 2$

Case B's father is known to be related to B's mother through B's father's father, but not through B's father's mother. Nevertheless, it appears on other evidence at least equally probable that B's father received his defective gene from his mother. Similarly, the situation for C's sibship is ambiguous. C's father's father is very probably $(gx)(Gy)$, and on this assumption C's father could be $(gx)(Gy)$ with probability $1 - \chi$, or $(Gx)(gy)$ with probability χ. Assuming, however, that B's father and C's father are both $(Gx)(gy)$, we have a distribution of children most favorable to the hypothesis:

Children:	normal ♂♂	affected ♂♂	normal ♀♀	affected ♀♀
Probability:	$\frac{1}{4}(1 + \chi)$	$\frac{1}{4}(1 - \chi)$	$\frac{1}{4}(2 - \chi)$	$\frac{1}{4}\chi$
Observed:	$a = 0$	$b = 2$	$c = 2$	$d = 0$

Since the sibships have been selected because each contains at least one affected child, Haldane computes the cross-over frequency from the totals for the affected and normal children separately. The former give an estimate $\chi = d/(b + d) = 0.4000$, with $(b + d)^3/bd = 20.8333$ units of information, while the latter give $\chi = (2a - c)/(a + c) = 0.0909$, with $(a + c)^3/9ac = 5.2817$ units of information. Now, having considered C's father to be $(Gx)(gy)$, we must then count him as a cross-over, since his father may be assumed to be $(gx)(Gy)$, although the 2 sisters of C's father would then be non-crossovers. We have thus a third estimate $\chi = 0.3333$, with $(1 + 2)^3/2 \cdot 1 = 13.5000$ units of information.

Combining the three sources of information, we obtain a weighted estimate $\chi = 0.336$, with information 39.6150, or standard error $(39.615)^{-\frac{1}{2}} = 0.159$. The deviation from random assortment ($\chi = 0.5$) is in the direction favoring linkage, but cannot be considered significant. Furthermore, in this calculation we have made a number of assumptions most favorable to the linkage supposition; in a more exact treatment, we would have to consider the alternatives, assigning probability weights to each set of assumptions. Consequently, as stated above, the pedigree does not appear to contain significant evidence for partial sex-linkage, and we may conclude that the gene for Gaucher's disease is more likely on one of the autosomes.

The conclusion that an autosomal recessive gene is responsible for this condition is in accord with previous reports. Snyder (1941) suggests that the condition is recessive. Gaucher's disease has long been regarded as "familial" and there have been numerous reports of cases in siblings, the first of these being given by Collier (1895). As many as five cases have been described in one

sibship (Woringer, 1934), and about one-third of the 89 cases collected by Hoffman and Makler (1929) has an affected sibling. The only report of cases in cousins known to the writers is that of Bloem, Groen and Postma (1936), who reported cases in half-first cousins; possible consanguinity of the parents was not mentioned. Cases in the first and third generations of a family are described by Anderson (1933). We are unable to find any reports in the literature suggesting the action of dominant or sex-linked genes.

SUMMARY

1. Five closely related cases of Gaucher's disease are described in a Negro kindred, the diagnosis being proved by autopsy in four cases. Two of these cases were previously reported by Pachman (1938).

2. The pedigree of this family is presented, showing the five cases to be in five separate but closely related sibships, with the parents of four of the affected children being second cousins.

3. It is concluded that Gaucher's disease is due to the action of an autosomal recessive gene which in the homozygous state causes an intracellular metabolic defect resulting in the deposit of kerasin in the cells of the reticulo-endothelial system. A brief review of the literature indicates that evidence presented in other reports is compatible with this conclusion.

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A Clinical and Genetical Study of Anencephaly[1]

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INTRODUCTION

ANENCEPHALY, rhachischisis, cranioschisis, acrania, holoacrania, etc., constitute a series of brain anomalies having presumably a common origin. The basic developmental failure is a defective closure of the medullary plate. The deficiencies in skeletal and muscle development seem to be only secondary to this primary anomaly of the central nervous system. The different names given above therefore should correspond to different types of manifestation only.

There is no need here to go into morphological or developmental details. For an evaluation of the correctness of the above conclusion the reader is referred to the papers by Ernst (1909), Ströer and van der Zwan (1939), and Bonnevie (1940).

It is evident that studies of developmental anomalies in human embryos are extremely difficult to perform. The scarcity of facts forces us to devise working hypotheses on evidence from experimental studies on animals. No doubt the condition of pseudencephaly, thoroughly studied in the mouse by Bonnevie (1936), is closely related to anencephaly in man. As this study in many respects formed a starting point in the present investigation some of the facts may be mentioned briefly.

Pseudencephaly in the mouse is primarily connected with disturbances in the development of the two germ layers. Major disturbances lead to the death of the embryo at that stage. If the disturbances are less pronounced the embryo may survive but with a defective and arrested development of the chorda plate and the medullary tube. If the disturbances are very slight a restitution may follow and the embryo develops further. In some cases, however, the result will be an open defect of the medullary tube in the mesencephalic region. Owing to the strong flexion of the neural tube this part of the brain is turned inside out. Thus the typical picture of pseudencephaly (which closely corresponds to anencephaly in man) arises secondarily from purely mechanical factors.

The evidence brought forward by Bonnevie shows that pseudencephaly is a developmental anomaly which in most cases causes the death of the embryo at an early stage, followed by disintegration and absorption *in utero*. Then, if we make the assumption that this condition is the effect of a simple recessive gene, we should *a priori* not expect clear-cut mendelian ratios within the litters. Among embryos up to 6 mm. length Bonnevie found

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17.5 per cent abnormal and among older embryos only 8.3 per cent. Among 30 pseudencephalics studied by the same author, not one developed up to full term.

The theory of Bonnevie that pseudencephaly in her material arose after a spontaneous mutation and that the condition was transmitted as the effect of a recessive autosomal lethal gene seems very well founded.

The hereditary pseudencephaly of the mouse produced by Snell and coworkers (*cf.* Snell & Picken, 1935) in X-ray experiments shows the same morphological and developmental characteristics. However, in this case it is very likely that gross chromosomal abberations lie behind the defect, i.e., translocations or chromosome deficiencies.

We also want to stress the well known fact that conditions similar to or identical with pseudencephaly-anencephaly have repeatedly been induced in various embryos (e.g. frogs and mice) with the aid of external agents (e.g. by changing the osmotic pressure of salt solutions in which the embryos develop and by X-rays.) Inasmuch as these experiments do not involve genic or chromosomal changes, the resulting anomalies may be regarded as *phenocopies*. The production of such phenocopies is naturally not contradictory to the fact that in other cases the same condition may be hereditary.

Anencephaly in Man

Most anencephalics in man are stillborn or if born alive live only for a few hours. The pregnancies usually terminate before full term. Delivery is practically always spontaneous. According to Suabedissen (*op. cit.* Hiilesmaa, 1945) delivery in 80 per cent of the cases took place between the 191*st* and 270*th* menstruation day when the fetal weight was from 1,000 to 2,500 g. and its length varied between 24 and 48 cm.

Turning to the question of the frequency of anencephaly, we have to consider the fact that the available figures give only the obstetrician's point of view. The frequency with which anencephalics appear in obstetric departments may be easily measured, but this is of course only one side of the problem, as it tells us nothing about the occurrence of anencephaly in the early stages of pregnancies and especially among aborted embryos.

Malpas (1937) obtained a figure of 0.308 per cent anencephalics among 13,964 deliveries in Liverpool during the period 1923–32. Ballantyne (*op. cit.* Dunn & Salter, 1944) found 1 case of anencephaly in 1,460 deliveries (0.068 per cent). Hiilesmaa (1945) gives a frequency of 0.30 per cent among 11,425 deliveries in Viipuri and 0.03 per cent among 17,084 deliveries in Helsinki.

As for the etiology of anencephaly, highly different opinions are to be found in the literature. On the one hand, we find Mall's (1917) categoric declaration (p. 70): "It is perfectly clear that monsters are not due to germinal and hereditary causes but are produced from normal embryos by influences which are to be sought in the environment." A similar opinion was put forward by Ossenkopp (1932). On the other hand a number of authors have discussed heredity as a probable etiological factor, e.g. Hammer (1933), Josephson and Waller (1933), Malpas (1937), Schade (1939), Dunn and Salter (1944), and Penrose (1946). With the exception of the studies by Malpas and Penrose, these papers

concern highly selected cases wherein two or more cases of anencephaly were found in the same family, or, as in the paper by Josephson and Waller, in identical twins. These observations therefore cannot be used as definite evidence for or against heredity.

Malpas' (1937) communication deals with 13,964 deliveries among which 44 cases of anencephaly were found (0.308 per cent). He concluded that the age of the mother might be of importance as the percentage incidence of anencephaly was 10 times greater in the maternal age group 46–50 than in the age group 16–20. The family data were based on questionnaires sent to the parents. It was found that the percentage incidence of anencephaly among the other members of the fraternities which contained one anencephalic was 2.6 as compared with an incidence in the general population of 0.308. In no case were the parents first or second cousins. Most interesting is Malpas' observation that the mothers of the anencephalics had a higher incidence of abortions. He gives the figure of 12 per cent, against 6 per cent in the general population.

Penrose's report (1946) deals with a study of 21 cases of anencephaly belonging to 20 different sibships. In these fraternities a total of 55 pregnancies resulted in 7 abortions (12.7 per cent), 1 stillborn of unknown cause, 2 cases with spina bifida (3.6 per cent), 1 case of anencephaly (1.8 per cent) and 44 non-malformed babies. In one family the parents were first cousins. In this paper, anencephaly, spina bifida and congenital hydrocephalus were statistically treated as equivalents. The analysis led Penrose to the conclusion that his figures indicate "a slight but significant tendency for the conditions to be duplicated in the families" (p. 73). Furthermore his calculations indicate that advancing maternal age is significantly related to the incidence of this *group* of malformations.

The data so far available, presented by various authors, scanty as they are, may be summarized as follows:

1. No one has ever been able to demonstrate an exogeneous etiological factor in anencephaly.
2. The incidence of anencephaly among the sibs of anencephalic propositi is slightly but probably significantly raised.
3. There is no doubt a causal connection between anencephaly and spina bifida.
4. The higher incidence of abortions among offspring of mothers of anencephalic propositi seems to be significant.
5. There is a peculiar sex ratio, with excesses for the female sex, as will be discussed further in this paper.
6. Most cases of anencephaly obtained from obstetric departments are premature.
7. Not a single fact has been produced containing evidence definitely against a genetical etiology.

Sex Incidence in Anencephaly

It has long been recognized that most anencephalics coming to observation are of female sex. Table 1 shows a compilation from the available literature.

The sex ratio in this material is about 3 ♀ : 1 ♂. There are at the moment no data available which could explain these findings. It may be that the majority of the anencephalic male embryos die at a very early stage and are expelled or the cause may be sought in a relatively strong sex limitation in the manifestation of the trait.

TABLE 1

AUTHOR	FEMALE	MALE	UNKNOWN SEX
Ballantyne, 1904	30	10	6
Malpas, 1937	31	13	—
Murphy, 1936 (*op. cit.* Dunn & Salter, 1944)	74	27	—
Angevine, 1938	13	6	1
Hiilesmaa, 1945	34	5	—
Penrose, 1946	16	2	3
Total	198	63	10

TABLE 2

DIAGNOSIS	LENGTH OF EMBRYO mm.	AUTHOR	NOTES
Anencephaly + spina bifida	14	Mall, 1917	All these embryos were obtained as spontaneous abortions or after hysterectomies and were dead at the observation
Anencephaly	13.5		
Anencephaly	15		
Anencephaly	6		
Anencephaly + spina bifida	24		
Anencephaly + spina bifida	27		
Anencephaly + spina bifida	2.1		Obtained as above but still alive at the observation
Anencephaly	190	Mall, 1917	
Anencephaly + spina bifida	10	Harbeson, 1939	Spontaneous abortion
Anencephaly	16.5	Dodds & De Angelis, 1937	

Anencephaly in Early Pregnancy

The fact that anencephaly has been observed repeatedly in pregnancies which terminated at an early stage in the death of the embryo is of particular interest. It appears to show that anencephaly undoubtedly is a causal factor in spontaneous abortion or, more generally, in early intrauterine fetal death. Available data do not permit an estimation of the frequency with which fetal death due to anencephaly or allied disturbances occurs. Nevertheless, such deaths appear to be not too uncommon. In Mall's (1917) material of human embryos with localized anomalies almost 40 per cent belong to the cranio-rachischisis group. Table 2 shows a compilation of anencephalics diagnosed at an early stage.

THE PRESENT INVESTIGATION

The problem set forth in this study was to collect evidence for or against a genetical etiology in anencephaly. It is closely connected with the search for lethal genes in human populations. In such studies it does not seem to be correct to collect a number of malformations or monsters of highly different appearance which may be and probably are of an entirely different etiology. The correct method should be to concentrate in the first place on well recognized clinical or pathological entities one by one. As our experience in medical genetics tells us, this, of course, does not mean that there will be any guarantee of a biological relation between a clinical and a genotypical entity; nevertheless, this way of proceeding probably will give a better result.

This is the reason why we have started with anencephaly alone as an easily recognized pathological condition. At the outset of the study the following questions were raised:

1. Will the examinations of the mothers or their anamnestic data, particularly during pregnancy, reveal any condition which may have a bearing on the birth of an anencephalic child?

2. Is it possible to find data which point to a genetical etiology? For practical reasons the family research work was limited to parents and sibs.

The Present Material

Every case of anencephaly born at the Obstetric Department, University Clinic of Lund, from 1923 to 1945 and at the Obstetric Department, University Clinic of Malmö, from 1917 to 1947 has been registered by Dr. O. Benoni-Nilsson. For placing this material at our disposal we are indebted to him and to the heads of these clinics, Professors A. Sjövall, M.D., and S. Genell, M.D., respectively. Altogether 67 cases were registered as *propositi*. These cases belonged to 67 different families. A family record was made for each propositus and the addresses of parents and sibs were traced in the parish registers. The geographic distribution of the present material is limited to the southern part of Malmöhus Län (south-western Skåne, Sweden) as concerns the domiciles of the mothers at the time the anencephalic child was born (table 3).

Of these original 67 families we were able to visit and examine personally 46 families. The remaining 21 had to be excluded for one of the following reasons: 1) the mother was deceased, 2) the family had moved to distant parts of the country or abroad, or 3) the family refused to cooperate (12 families).

To secure a uniform judgment, these 46 families were visited and examined by us personally, and all hospital records were studied. As for the clinical examination and the anamnesis, the following data were considered important.

Anamnesis: Medical histories were secured, with special reference to 1) con-

sanguinity between the parents, 2) complete clinical history of every person, 3) the condition of the mothers during each pregnancy, with special reference to German measles and other virus diseases, 4) a history of syphilitic infection,

TABLE 3. DISTRIBUTION OF CASES OF ANENCEPHALY BY YEARS, AS OBSERVED AT THE OBSTETRICAL DEPARTMENTS OF THE UNIVERSITY CLINICS AT MALMÖ (1917–1947) AND AT LUND (1923–1945)

MALMÖ				LUND			
Year	Number of deliveries	Anencephalics		Year	Number of deliveries	Anencephalics	
		Number	Per Cent			Number	Per Cent
1917	1279	1	0.08	1917	—	—	—
1918	1081	0	0.00	1918	—	—	—
1919	1079	1	0.09	1919	—	—	—
1920	1508	2	0.13	1920	—	—	—
1921	1261	1	0.08	1921	—	—	—
1922	1195	0	0.00	1922	—	—	—
1923	1144	3	0.26	1923	1643	1	0.06
1924	1273	2	0.16	1924	1707	0	0.00
1925	1254	0	0.00	1925	1716	1	0.06
1926	1245	2	0.16	1926	1740	1	0.06
1927	1160	3	0.26	1927	1702	2	0.12
1928	1233	1	0.08	1928	1931	0	0.00
1929	1201	0	0.00	1929	1874	0	0.00
1930	1302	3	0.23	1930	2117	1	0.05
1931	1399	0	0.00	1931	2059	3	0.15
1932	1306	0	0.00	1932	2090	1	0.05
1933	1239	0	0.00	1933	1838	0	0.00
1934	1407	2	0.14	1934	1983	0	0.00
1935	1497	3	0.20	1935	1952	0	0.00
1936	1701	1	0.06	1936	2038	1	0.05
1937	1841	3	0.16	1937	2271	1	0.04
1938	2013	2	0.10	1938	2316	2	0.09
1939	2232	1	0.04	1939	2362	2	0.08
1940	2284	1	0.04	1940	2320	3	0.13
1941	2503	0	0.00	1941	2097	0	0.00
1942	2920	0	0.00	1942	2367	0	0.00
1943	3240	1	0.03	1943	2503	4	0.16
1944	3492	3	0.09	1944	2714	1	0.04
1945	3477	1	0.03	1945	2866	3	0.10
1946	3445	2	0.06	1946	—	—	—
1947	3422	1	0.03	1947	—	—	—
Total	56633	40	0.07 ±0.01		48179	27	0.06 ±0.01

5) any mechanical interference during pregnancy (e.g. attempt to provoke abortion), 6) a history of Rh-incompatibility.

Clinical examination: Every person showing signs or symptoms of disease

was examined physically and/or neurologically and/or mentally with the usual bedside equipment.

According to our original plan the mothers were tested for the Rh factor. For the serological examination we are indebted to Rune Grubb, M.D., Bacteriological Institute, Lund. However, when it was found that among the 10 first tested mothers 8 were Rh positive and only 2 Rh negative, this test was omitted as probably having nothing to do with the present problem.

The Wassermann test was performed in a few mothers not previously tested at the hospitals during pregnancy. They were all negative. We are indebted to Professor Arvid Lindau, M.D., for these tests.

Frequency of anencephaly in the present material. Our material comprises altogether 104,812 deliveries among which 67 cases of anencephaly were recorded. This gives a frequency of 0.064 per cent. As seen in table 3 the difference between the material obtained in Malmö and Lund is not significant. The difference between our figure and the figures given by previous authors (see p. 62) is probably accidental.

The Propositi

Some clinical data concerning the 67 propositi of the present material have been summarized in table 4.

Duration of pregnancy. In 64 cases sufficient data were obtained to form an estimate of the duration of the pregnancy. The mean value was 265.5 days counted from the end of the last menstruation. This is close to the normal average of 270 to 280 days. The duration of normal pregnancies, however, may vary within rather wide limits and is usually given as 230 to 330 days. As seen in table 4, most of the cases fall within these limits, but 15 of them or about 23 per cent were below 230 days. No doubt this allows the conclusion that there is a marked tendency to premature births in anencephalic pregnancies.

As length of pregnancy and clinical estimation of the development of the fetus will decide whether the patient goes to the obstetrical or to the gynecological department (the latter taking care of all cases considered to be abortions) the material is naturally biased for these two factors. In other words, the shortest pregnancies have been excluded. In spite of this the tendency is obvious.

Hydramnion. A conclusive hydramnion was recorded in 33 cases, i.e., in about 50 per cent. This only confirms previous observations that hydramnion is one of the commonest signs in anencephalic pregnancies as is also the case in other pregnancies with a malformed fetus. The possible etiological significance of hydramnion has been discussed at length in previous literature. The conception of today concerning malformations of the embryo is that an increase in the amount of liquor amnii beyond the normal limits cannot be claimed as an etiological factor, but may rather be considered as a consequence of the pathological condition of the fetus. Hydramnion in anencephaly suggests that a direct tran-

TABLE 4

FILE NO.	HYDRAMNION	DURATION OF PREGN.	DEAD BEFORE DELIVERY	BORN ALIVE AND DIED AFTER	WEIGHT (G.)	LENGTH (CM.)	SPINA BIFIDA	SEX
KKL								
91/23	+	264		55 min.	2760	46		♀
348/25		301		25 min.	3020	48		♂
1740/26		287		2 hours	1210	46		♀
824/27		244	+		1160	27	+	♀
1190/27		323	+		3520	51		♂
1772/30		288	+		2670	42	+	♀
1768/31	+	242		1 min.	1210	34	+	♀
2090/31	+	249	+		1560	41		♀
2121/31	+	227		10 min.	1150	32		♀
235/32		249		30 hours	3150	?		♂
1620/36	+	298	+		4070	56		♀
1676/37	+	330		3 hours	3300	45.5		♀
125/38		253	+		2030	45		♂
388/38	+	259	+		1740	39		♀
410/39	+	229	+		?	?		♂
2347/39	+	237		1 hour	1660	40		♀
513/40	+	313	+		4550	53		♂
1385/40		262	+		?	?		♂
2717/40		214	+		680	24		♀
2541/43	+	229	+		?	?		♀
3511/43	+	250	+		1400	39		♀
3793/43	+	311	+		4300	53.5		♂
4081/43		?	+		?	?		♂
2556/44	+	272		22 hours	2450	43		♂
1365/45		295	+		3000	49		♂
3318/45	+	211	+		1300	43		♂
4416/45	+	296	+		2300	44		♀
KKM								
645/17		260		27 hours	2900	47		♂
1134/19	+	272	+		2500	48		♀
661/20	+	257		2 hours	1830	?		♀
664/20		345	+		3560	52		♀
1088/21		256	+		1800	40		♀
788/23		330		20 hours	3400	46		♀
1014/23		225	+		1330	38		♀
1161/23	+	?	+		2150	48		♂
621/24		263	+		1400	?		♀
662/24		226		5 hours	1250	37		♂
7/26		276		3 hours	3860	51		♀
1667/26	+	284	+		1670	38		♀
278/27		254	+		860	28	+	♀
1205/27	+	232	+		2000	41		♂
1558/27	+	197	+		670	31		♀
1199/28		229	+		1020	26	+	♀
440/30	+	271	+		1320	39		♀
1292/30		297	+		3400	52		♂
1700/30		244	+		1045	38		♀

TABLE 4.—*Continued*

FILE NO.	HYDRAMNION	DURATION OF PREGN.	DEAD BEFORE DELIVERY	BORN ALIVE AND DIED AFTER	WEIGHT (G.)	LENGTH (CM.)	SPINA BIFIDA	SEX
1174/34	+	242	+		1630	32	+	♀
2042/34		208	+		700	34	+	♀
834/35	+	204	+		995	25	+	♀
851/35	+	234	+		1000	34	+	♂
1522/35	+	220	+		900	35	+	♀
128/36	+	349	+		1520	35		♀
1798/37	+	222	+		1330	41		♂
1823/37		?	+		?	26		?
2301/37		210	+		395	27		♂
769/38	+	251	+		1710	44		♂
2023/38		303		14 hours	3600	45		♀
1485/39	+	276		45 min.	1705	46		♀
2236/40		324	+		1370	42	+	♀
619/43		310	+		3200	53		♀
1173/44		308		6 hours	3300	53		♀
1999/44		234		10 min.	1320	36		♂
2275/44		297		1 min.	3350	52		♀
2032/45		334	+		3100	52		♀
962/46		266	+		1800	38	+	♀
1463/46	+	219	+		950	37		♂
3512/47	+	328		35 hours	3580	57		♂
Total.....	33		47				12	42♀:24♂:1Δ

sudation of fluid may occur from the exposed nervous structures which have the same epiblastic origin as the amniotic epithelium.

Anencephaly. The sex distribution in the present material was 42 females: 24 males: one case of unknown sex. This corresponds to a sex ratio of about 2♀ : 1♂. The excess for the female sex thus is a little less in our material but still pronounced (cf. table 1).

Forty-seven propositi died before or during delivery. The remaining lived only for a short period varying from a few minutes to 35 hours.

The weight at birth has been recorded in 62 cases, the mean value being 2090.5 g., which is considerably below normal. The total length was recorded in 60 cases, the mean value being 41.4 cm.

The diagnosis of anencephaly needs no further comment as the condition is easily recognized, and a discussion of the variability of its manifestation is out of the scope of this paper. We only want to stress the fact that in 12 cases the brain defect was connected with a spina bifida aperta. These findings, which are in complete agreement with previous communications, may point to a causal connection between the two conditions.

Prematurity. As outlined above, anencephaly has repeatedly been observed

as a cause of fetal death in early pregnancy. Therefore, it is of particular interest to see how many will show full term development in an obstetrical series like the present one. We accept the following conventional definitions and limits. Concerning weight, if this is less than 2,500 g. the child is considered premature. Concerning length, the upper limit for abortion is 35 cm.; for prematurity, 47 cm.; and over 47 cm. is considered full term development. These figures will account for all fetuses without gross malformations. In anencephaly the malformation inevitably causes a reduction of weight due to the lack of brain tissue and also a reduction of length due to the skull defect. In a comparison with the development of normal fetuses this should in some way be corrected for.

The weight of the brain in the newborn is about 10 per cent of the total body weight. In anencephaly not all of the nervous tissue is lacking, but, on the other hand, the skull is defective. Presumably about 5 cm. of the length is lost in a full term anencephalic child due to the defect of the skull and the shortened

TABLE 5. DEVELOPMENT OF THE ANENCEPHALICS OF THE PRESENT MATERIAL ACCORDING TO THE WEIGHT AND LENGTH OF THE FETUS

Weight (grams):

250–750	750–1,250	1,250–1,750	1,750–2,250	2,250–2,750	2,750–3,250	3,250–3,750	over 3,750	Total
4	11	17	6	4	7	9	4	62

Length (centimeters):

20–25	25–30	30–35	35–40	40–45	45–50	50–55	over 55	Total
1	6	6	12	11	12	10	2	60

neck. Therefore it seems reasonable to estimate that about 10 per cent of the weight and 10 per cent of the length are lost due to the malformation. The limit between premature and full term development has to be lowered correspondingly. From table 5 it can easily be seen how many fetuses may be considered premature according to any chosen limit. We think it justified to judge fetuses below 2,250 g. in weight or below 40 cm. in length as not fully developed. This would give a figure of about 40 to 60 per cent premature anencephalics in this material. Even if we lower the limit to 1,750 g. and 35 cm., this will still give a figure of 20 to 50 per cent unquestionably premature fetuses. There is thus even in obstetrical material a strong tendency toward premature birth in anencephaly.

The Mothers of Anencephalics

Anamnestic data. Complete anamnestic data have been obtained for the 46 mothers who have been visited and examined by us. An analysis of these data has not given the slightest indication that any special clinical or pathological condition of the mother may have a connection with the birth of the anence-

phalic child. 31 mothers claimed that they always had been perfectly healthy up to the time when the anencephalic was born.

Condition during anencephalic pregnancy. According to the 67 clinical records, of which 46 cases were completed by personal inquiry, 51 mothers had no disorders whatsoever during pregnancy. In the remaining 16 cases the following conditions, apparently without significance as for the etiology of anencephaly, have been recorded:

Albuminuria, 3 cases
Diabetes mellitus, 1 case
Periodic vomiting + swollen legs, 1 case
Edema of the legs + slight albuminuria, 1 case
Arterial hypertension, 1 case
Medium anemia, 3 cases
Edema of the legs without albuminuria, 2 cases
Visual disturbances + edema of the legs + albuminuria, 1 case
Cystopyelitis, 1 case
Thrombosis of left leg, 1 case
Oophoritis, 1 case.

All of these are conditions often met with in pregnancies which terminate with the birth of a normal baby, and we do not think they represent anything of significance.

No evidence of syphilitic infection has been obtained in any case. A special inquiry as to infection with German measles during early pregnancy gave a completely negative result. As mentioned above, a search for Rh-incompatibility as a possible etiological factor gave a negative result too.

Maternal age. Maternal age has often been claimed as a factor in human congenital malformations (Penrose, 1946, and others). As far as we know, it has hitherto been clearly demonstrated beyond doubt only in mongoloid idiocy, for we cannot accept calculations based upon a collection of different malformations which may have a quite different etiology.

For the following statistical analysis we are indebted to Professor C. E. Quensel, F. D., and to Mr. H. Ambjörn, F. K., who helped calculate tables 7-10.

The age distribution of the mothers of the propositi has been compared with the normal distribution during 1916–1945 in the same area (Malmöhus Län) as that from which the propositi were collected. Children born in and out of wedlock have been treated separately.

The actual age distribution on which the analysis was based is shown in tables 6–9. The results of the statistical analysis appear in tables 10 and 11.

We have reached the conclusion that maternal age is undoubtedly *not* of significance in anencephaly. As for illegitimate anencephalics the material is too small to allow a chi-square calculation but the correspondence between observed and expected figures is nevertheless good.

The distribution of the anencephalics of married and unmarried women is likewise in good correspondence with the expected figures (cf. table 11).

The Sibships of the Anencephalic Propositi

Suppose that anencephaly were caused by a single recessive gene (point mutation or chromosome deficiency) with complete manifestation and that this

TABLE 6. MATERNAL AGE OF ANENCEPHALIC CHILDREN BORN INTRAMATRIMONIALLY (3 CASES HAVE BEEN EXCLUDED AS OFFICIAL STATISTICAL FIGURES FOR COMPARISON LATER THAN 1945 ARE NOT AVAILABLE)

AGE OF MOTHERS, (YRS.)	DISTRIBUTION OF ANENCEPHALICS ACCORDING TO 5 YEAR PERIODS 1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	TOTALS
15–20	—	—	—	1	—	—	1
20–25	1	1	2	3	2	3	12
25–30	1	1	3	1	4	3	13
30–35	1	4	1	2	4	1	13
35–40	1	1	2	—	3	3	10
40–45	—	—	—	—	2	1	3
Totals.....	4	7	8	7	15	11	52

TABLE 7. MATERNAL AGE OF ALL CHILDREN BORN INTRAMATRIMONIALLY IN MALMÖHUS LÄN, SWEDEN (THE INVESTIGATION AREA). ACCORDING TO SWEDISH OFFICIAL STATISTICS

AGE OF MOTHERS, (YRS.)	DISTRIBUTION OF CHILDREN ACCORDING TO 5 YEAR PERIODS 1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	TOTALS
–20	474	633	658	643	855	1158	4421
20–25	7411	7316	6808	6203	7301	9715	44754
25–30	12011	11148	9538	9077	10548	13751	66073
30–35	9687	9282	7774	6790	8211	11404	53148
35–40	7287	6535	4996	4179	4360	6189	33546
40–45	3199	2796	2181	1624	1492	1682	12974
45–50	247	248	214	140	132	125	1106
50–55	—	—	—	—	1	—	1
Totals.....	40316	37958	32169	28658	32900	44024	216023

gene did not cause an interruption of the pregnancy before full term. Then we should expect to find about 25 per cent anencephalic children among the sibs. Evidently it is not as simple as that. Anencephaly is repeated in the sibships with a very low frequency in the neighborhood of 1 per cent (cf. Penrose, 1946). However, if we consider a gene having a lethal effect mainly at an early stage during embryonal development, any percentage between 0 and 25 may be found. Thus the fact that a congenital defect is repeated in the sibships with

a very low frequency is by itself no conclusive evidence against a genetical etiology.

In the foregoing we have been trying to show that anencephaly very often causes the interruption of the pregnancy before term and that many anencephalic pregnancies end with early abortions. Thus, assuming a simple recessive gene, a frequency of 25 per cent is not to be expected. On the other hand, we should expect a relatively high frequency of abortions in the sibships of the propositi.

TABLE 8. MATERNAL AGE OF ANENCEPHALIC CHILDREN BORN EXTRAMATRIMONIALLY

AGE OF MOTHERS, (YRS.)	DISTRIBUTION OF ANENCEPHALICS ACCORDING TO 5 YEAR PERIODS 1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	TOTALS
15–20	—	—	1	—	1	—	2
20–25	—	—	3	2	—	2	7
25–30	—	1	—	—	1	—	2
30–35	—	—	1	—	—	—	1
Totals	0	1	5	2	2	2	12

TABLE 9. MATERNAL AGE OF ALL CHILDREN BORN EXTRAMATRIMONIALLY IN MALMÖHUS LÄN, SWEDEN (THE INVESTIGATION AREA). ACCORDING TO SWEDISH OFFICIAL STATISTICS

AGE OF MOTHERS, (YRS.)	DISTRIBUTION OF CHILDREN ACCORDING TO 5 YEAR PERIODS 1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	TOTALS
–20	1484	1694	1866	1655	1602	1494	9795
20–25	3571	3494	3390	2791	2258	2053	17557
25–30	1660	1474	1300	1040	821	829	7124
30–35	817	655	509	409	409	435	3234
35–40	455	394	279	217	213	256	1814
40–45	162	152	112	85	70	86	667
45–50	11	13	9	4	4	4	45
Totals	8160	7876	7465	6201	5377	5157	40236

Calculations According to the Propositus Method of Weinberg

In 4 families there are twin pairs and in 3 cases one of the twins was an anencephalic. Since conclusive evidence about these pairs being mono- or dizygotic is lacking in every case, we think it better to exclude these families from the calculations.

There remain 42 families. After the usual exclusion of the propositi we find here 86 children born alive and without any malformation, 1 stillborn of unknown cause (no malformation), 1 child with rachischisis (stillborn) and 22 spontaneous abortions. Thus, if we consider craniorachischisis as an entity,

this condition was found in the sibships with a frequency of 0.9 per cent. However, the frequency of spontaneous abortions among the mothers of anencephalic propositi is 20 per cent. As for the craniorachischisis group, the empirical risk figure found here is lower than that given by Penrose (1946), but considering that we are forced to deal with small numbers we may for practical purposes preliminarily state:

If a woman has borne a child with anencephaly the mean risk figure that any subsequent pregnancy will result in another full-term or nearly full-term baby with a craniorachischisis malformation is about 1 per cent. However, the risk that such a pregnancy will end with spontaneous abortion is about 20 per cent.

TABLE 10. STATISTICAL ANALYSIS OF MATERNAL AGE OF ANENCEPHALICS AS COMPARED WITH THE TOTAL POPULATION OF BIRTHS FROM TABLES 7 AND 9

BORN INTRAMATRIMONIALLY			BORN EXTRAMATRIMONIALLY		
Age of mother (years)	Observed	Expected	Age of Mother (years)	Observed	Expected
15–25	13	11.84	15–20	2	2.92
25–30	13	15.90	20–25	7	5.24
30–35	13	12.79	25–30	2	2.12
35–45	13	11.20	30–35	1	0.96

$\chi^2 = 1.20$, D.F. = 3.

TABLE 11. ANENCEPHALICS BORN INTRAMATRIMONIALLY AND EXTRAMATRIMONIALLY COMPARED WITH THE TOTAL POPULATION OF BIRTHS

	EXTRAMATRIMONIAL	INTRAMATRIMONIAL	TOTAL
Anencephalics	12	52	64
Total births	40,236	216,023	256,259

$\chi^2 = 0.45$, D.F. = 1.

SOME GENETICAL CONSIDERATIONS

As we have some reason to suspect that the aborted embryos produced by the mothers of anencephalic full term babies really contain anencephalic embryos it may be justified to add a genetical analysis based on this hypothesis. Furthermore, we assume that we are dealing with a simple recessive lethal gene. The material, i.e. the 46 completely examined sibships used here, will be found in table 12. The expected number of affected individuals (by which is meant here the abortions too) for every different sibship size can be calculated from the expansion of $(a + 3b)^n$ and omitting sibships expected to have only normal members. These latter would naturally never appear in any sample of this kind. For the principles of this calculation the reader is referred to Macklin

(1938). The analysis, summarized in table 13, appears to show that the distribution is such as might be expected in simple recessive inheritance.

TABLE 12. SYNOPSIS OF THE 46 COMPLETELY EXAMINED SIBSHIPS

Legend:

Nm Male, no malformation.
Nf Female, no malformation.
Am, *Af* Anencephalus, male, female respectively.
Au Anencephalus, unknown sex.
Asm, *Asf* Anencephalus with spina bifida, male, female respectively.
Sm Spina bifida, male.
Dm, *Df* Stillborn, cause unknown, male and female respectively.
M Spontaneous abortion.
Fm, *Ff* Feebleminded male and female respectively.
Em Epilepsy, male.
Propositus in brackets. A dash between two individuals means twins.

File No. **KKL**		*File No.* **KKM**	
91/23	*Nf Fm* (Af)	1134/19	*Nf* (*Af*)
348/25	*Nf* (*Am*) *Nf Nf Nf*	661/20	*Nf*-(*Af*) *Nm Nm*
1740/26	*Nf Nm* (*Af*) *Nm Nm*	788/23	*Nm Nf* (*Af*)
824/27	(*Asf*) *Nf*	621/24	(*Af*) *Nf Nm Nf*
1772/30	(*Asf*) *Nf* M M M M	662/24	(*Am*)-*Dm*
2121/31	(*Af*)	278/27	(*Asf*) *Em Nf Nf*
1620/36	*Nf Nm Nm* (*Af*)	1205/27	*Nm Nf* (*Am*) *Nf Nf*
1676/37	*Nf Nf Fm Nf* (*Af*)	1558/27	(*Af*)
338/38	*Nm Nf Nm Nf Nm* (*Af*)	440/30	(*Af*) M *Nm Nf Nm Nm* M M
410/39	*Nf Nf Nm Nf Nf Nm*-(*Am*) *Nf*	1292/30	*Nf* M M *Nm Nm* (*Am*) *Nm*
513/40	*Nf Nm Nm Nf Nf* M M (*Am*) *Nf*	1174/34	(*Asf*) *Nf*
1385/40	(*Am*) *Nf Nf*	2042/34	(*Asf*) *Nm Nf*
2717/40	(*Af*) *Nm*	834/35	*Sm* (*Asf*) *Nm Nm Nm*
2541/43	*Nf* M M (*Af*) *Nm*	1522/35	(*Asf*)
3511/43	M M (*Af*) *Nm*	128/36	(*Af*) *Nf Nm* M M
3793/43	(*Am*) M *Nm*	1823/37	*Nm*-*Dm* (*Au*)
4080/43	*Dm* (*Am*) *Ff Nf*	2301/37	(*Am*) *Nm Nm Nf*
2556/44	*Nm* (*Am*) *Nf*	2023/38	(*Af*) *Nm*
1365/45	M M (*Am*) *Nm*	1485/39	(*Af*) M *Nm*
4416/45	M (*Af*)	2236/40	(*Asf*) *Nm Nm*
		1173/44	(*Af*) *Dm Nm*
		2275/44	*Nm Nf* (*Asf*)
		2032/45	*Nm* (*Af*)
		962/46	(*Asf*)
		1463/46	(*Am*) *Nf*
		3512/47	*Nm Nm* (*Am*)

A test according to Macklin's (1938) Percentage Affected Method is shown in table 14. The correspondence between observed and expected figures is very

good. However, it is more reasonable to assume that not all abortions have the same etiology. The slight tendency of an increase of the abortion rate in the larger sibships seen in table 14, and the slight accumulation on the last birth ranks (cf. table 19) may indicate that the etiology is not the same in all cases.

Suppose that only half the abortions are caused by the "anencephalic gene."

TABLE 13. DISTRIBUTION OF AFFECTED INDIVIDUALS (ASSUMING THAT ALL ABORTIONS RECORDED ARE ANENCEPHALICS) IN SIBSHIPS OF VARYING SIZE. EXPECTED FREQUENCIES ARE BASED ON THE EXPANSION OF $(a + 3b)^n$ (CF. MACKLIN, 1938).

NUMBER AFFECTED	SIBSHIP SIZE, n								TOTAL SIBSHIPS		$(O-c)^2/c$
	2	3	4	5	6	7	8	9	Observed O	Expected c	
1	8	10	6	4	1	0	1	0	30	27.09	0.31
2	1	2	0	1	0	0	0	0	4	11.18	
3	—	0	2	2	0	1	0	1	6	2.90	
4	—	—	0	0	0	0	1	0	1	0.65	
5	—	—	—	0	1	0	0	0	1	0.13	
6	—	—	—	—	0	0	0	0	0	0.02	0.57
7	—	—	—	—	—	0	0	0	0	0.00	
8	—	—	—	—	—	—	0	0	0	0.00	
9	—	—	—	—	—	—	—	0	0	0.00	
Total no. sibships.....	9	12	8	7	2	1	2	1	42	41.97	0.88

$\chi^2 = 0.88$, D.F. $= 1$, $P = 0.35$.

TABLE 14. SINGLE RECESSIVE TEST ACCORDING TO MACKLIN'S "PERCENTAGE AFFECTED METHOD." IT IS ASSUMED THAT ALL ABORTIONS IN THESE SIBSHIPS ARE GENETICALLY ANENCEPHALIC

NUMBER OF PREGNANCIES IN FAMILY	TOTAL NUMBER OF PREGNANCIES	AFFECTED CHILDREN		NORMAL CHILDREN		$\Sigma(O-c)^2/c$.
		Observed O	Expected c	Observed O	Expected c	
2	18	10	10.26	8	7.74	0.015
3	36	14	15.48	12	10.52	0.350
4	32	12	11.84	20	20.16	0.003
5	35	12	11.55	23	23.45	0.026
6–9	44	17	12.54	27	31.46	2.219
Total.....	165	65	61.67	90	93.33	2.613

$\chi^2 = 2.613$, D.F. $= 5$, $0.70 < P < 0.80$.

If we add these to the anencephalics and the spina bifida case, presumably being of the same origin, we would have 58 affected individuals out of a total of 169, or 34 per cent. This is still not far from what one might expect for a simple recessive lethal for an average family size of 3.7 children.

The possible mutation rate, assuming that the Hardy-Weinberg formula

would hold for this fairly common gene, would be 6.4×10^{-4} chromosome per generation, according to the frequency determined earlier in this paper. This would mean that one person out of every 770 had a mutation from the normal to the "anencephalic gene" (This does not include any abortions).

However, as presumed above, the manifestation of this gene would in most cases occur as spontaneous abortion. Considering the spina bifida case of this material as genetically anencephalic, only one case was recognized among a total of 110 from presumably **Aa** × **Aa** matings (cf. p. 73 and table 15). On the other hand, 22 abortions were found. Thus, taking the other extreme and considering all abortions as genetically anencephalic, the condition could be diagnosed only in one case out of 23 presumably **aa** lethals, or in other words there would be 23 times as many pregnancies with a genetically anencephalic embryo as appears from the apparent frequency in an obstetrical material.

TABLE 15. LETHAL OUTCOME OF PREGNANCIES FOR MOTHERS OF ANENCEPHALIC PROPOSITI IN THE PRESENT MATERIAL, COMPARED WITH PREGNANCIES OF 1400 MOTHERS OF NORMAL PROPOSITI SELECTED BY FILE NUMBER COVERING THE PERIOD 1925 TO 1945 AT THE OBSTETRIC DEPARTMENT, UNIVERSITY CLINIC OF LUND

PREGNANCIES WITH KNOWN OUTCOME	ABORTIONS & STILLBIRTHS (LETHAL)	BORN ALIVE (NON-LETHAL)	TOTAL
Anencephalic propositus	24	86	110
Normal propositus	265	3289	3554
Total	289	3375	3654

$\chi^2 = 30.3$, D.F. = 1, $P < 0.001$.

Now a minimum estimate of the rate of spontaneous abortions in the Swedish population is 10 per cent. Thus the 104,812 deliveries of this material would at least correspond to 116,458 pregnancies. The 67 anencephalics should all come from **Aa** × **Aa** matings, but some matings of the same type would produce a number of **aa** genotypes all of which result in abortions, and naturally some would produce **AA** and **Aa** genotypes only. We would expect in this sample 1474 (22 × 67) pregnancies with an anencephalic embryo which terminate with abortions. Thus among the total of 116,458 pregnancies, 1541 (1474 + 67) could be considered genetically anencephalic embryos. The frequency of **aa** lethal genotypes would be 1541/116,458 or about 1.3 per cent. This would mean a very high mutation rate of 1.3×10^{-2} chromosome per generation or one person out of every 40 would have a mutation. However, this does not necessarily imply the rate of mutation at a special locus. The nervous structures are very sensitive during early embryonic stages, and point mutations or chromosome deficiencies which occur at different loci may have the same effect on the development of the brain and spinal cord. In other words, anencephaly and

allied disturbances may result from single recessives at different loci. The mutation rate discussed here (6.4×10^{-4} to 1.3×10^{-2}) thus may be considered more as a collected rate for mutations at different gene loci affecting the development of the brain and spinal cord and producing a more or less similar pathological picture.

The estimate of about 11,646 spontaneous abortions belonging to the present sample of 104,812 pregnancies furthermore would mean that 1474/11,646 or about 12% of all spontaneous abortions would be caused by lethal mutations affecting the nervous system.

The considerations under this heading are obviously very speculative but it seems very important to stress such interpretations which may be checked by further research. Abortions and stillbirths may be caused by lethal factors

TABLE 16. LETHAL OUTCOME OF PREGNANCIES FOR MOTHERS OF ANENCEPHALIC PROPOSITI IN THE PRESENT MATERIAL, COMPARED WITH PREGNANCIES OF 59 MOTHERS OF NORMAL RECRUIT PROPOSITI SELECTED FOR STUDIES OF DENTAL CARIES

PREGNANCIES WITH KNOWN OUTCOME	ABORTIONS & STILLBIRTHS (LETHAL)	BORN ALIVE (NON-LETHAL)	TOTAL
Anencephalic propositus	24	86	110
Recruit propositus	27	205	232
Total	51	291	342

$\chi^2 = 6.3$, D.F. $= 1$, $P = 0.012$.

to a much greater extent than most obstetricians and gynecologists today are inclined to think.

The Frequency of Abortions

The figure of 20 per cent in the present material has to be compared with a normal material in order to decide if the deviation is significant. The situation is that among a number of women selected under the conditions given above, which includes that they are women capable of giving birth to normal children, the frequency is 20 per cent. This figure cannot be compared with the general frequency of abortion obtained by random selection of a number of women, as then also women not able to produce full term babies (i.e. cases with habitual abortions only) will be included.

To obtain a suitable control material we have selected by file number from 1925 to 1945, 100 mothers of normal babies for each year an anencephalic was born at the Obstetrical Department, Lund. This material was treated according to the propositus method, too. All abortions and stillborns had been carefully noted in the files.

In this comparison we have included all pregnancies with lethal (abortions

and stillborns) as well as non-lethal outcome. As is seen in table 15, the difference is statistically highly significant. In the control material the mean frequency of lethal outcome of pregnancies for women who have had at least one normal baby is 7.5 per cent.

As some error may arise from taking a control material in this way due to the fact that abortions may accumulate at the end of the fertile period (7.5 per cent is in fact abortions previous to the last normal child) we have also made a comparison with another control material of women who were beyond the reproductive period.

In another investigation carried out at our institute on dental caries, 59

TABLE 17. BIRTH RANKS OF ANENCEPHALIC PROPOSITI OF THE PRESENT MATERIAL. ABORTIONS ARE INCLUDED IN THIS CALCULATION

TOTAL NUMBER OF SIBS	NUMBER OF ANENCEPHALICS WITH BIRTH RANK 1	2	3	4	5	6	7	8	9	EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER FIRSTBORN	CORRECTED EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER LASTBORN
1	3	—	—	—	—	—	—	—	—	—	—	—	—
2	6	3	—	—	—	—	—	—	—	4.5	6.0	4.5	3.0
3	6	1	5	—	—	—	—	—	—	4.0	9.0	6.0	7.5
4	3	2	3	1	—	—	—	—	—	2.3	6.0	4.6	2.0
5	1	2	—	2	2	—	—	—	—	1.4	2.5	3.5	5.0
6	1	—	—	—	—	1	—	—	—	0.3	3.0	0.9	3.0
7	—	—	—	—	—	1	2	—	—	0.4		1.4	7.0
8	1	—	—	—	—	—	—	—	—	0.1	4.0	0.4	
9	—	—	—	—	—	—	—	1	—	0.1		0.5	
Totals.....	18 = *firstborn*								*lastborn* = 14	13.1	30.5	21.7	27.5

mothers of recruit propositi were thoroughly interviewed about their pregnancies. Lethal outcome was found in 11.6 per cent. The difference in comparison with the present material is still significant (cf. table 16).

We may thus state with considerable certainty that lethal outcome of pregnancies is more frequent in women who have had an anencephalic child.

The Birth Ranks of Anencephalics

When a trait is caused exclusively by genotypical factors it should be evenly distributed for all birth ranks, the first, second, third, etc., child having exactly the same chance to be affected. If, for instance, the first child is more often affected, birth trauma may be a factor; if it is the last, the age of the mother may have something to do with the condition.

The distribution of different birth ranks was tested according to the method of Weinberg and Schulz (cf. Schulz, 1936). When sibships with a different

number of siblings are summarized the sums of the expected figures for the different birth ranks should be compared with the corresponding sums of the observed figures. In this calculation we have only one anencephalic (the propositus) in each sibship. Children without sibs must be left out of consideration. The expected frequency for any birth rank is $\Sigma(a_n)/n$, where a_n is the observed number of affected individuals included in sibships of n members. By this it is assumed that each individual has the same chance for any particular birth position. Starting with the left half of table 17 the following expected figures have been calculated:

TOTAL NUMBER OF SIBS n	EXPECTED NUMBER OF ANANCEPHALICS WITH BIRTH RANK 1	2	3	4	5	6	7	8	9
1	—								
2	4.5	4.5							
3	4.0	4.0	4.0						
4	2.3	2.3	2.3	2.3					
5	1.4	1.4	1.4	1.4	1.4				
6	0.3	0.3	0.3	0.3	0 3	0.3			
7	0.4	0.4	0.4	0.4	0.4	0.4	0.4		
8	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
9	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total expected:	13.1	13.1	8.6	4.6	2.3	0.9	0.6	0.2	0.1
Total observed:	18	8	8	3	2	2	2	1	0

A chi-square test may be applied as follows:

BIRTH RANK	O	c	$(O-c)^2/c$
1	18	13.1	1.83
2	8	13.1	1.99
3	8	8.6	0.04
4–9	10	8.7	0.19
Totals	44	43.5	4.05

$\chi^2 = 4.05$, D.F. = 3, $0.20 < P < 0.30$

Consequently there is no objection to the assumption of a random distribution on the different birth numbers.

This calculation may be accepted as a reasonable estimation. However, it is affected with a minor incorrectness. If we want to score primogeniture against ultimogeniture the fact that the distance between the firstborn and the lastborn is a function of the number of siblings of each sibship must be taken into consideration. Thus, for instance, the difference between the firstborn and the lastborn must have a greater significance in a sibship of ten members than in a sibship of two only.

If we examine further especially the frequency of firstborn anencephalics as compared with lastborn the following correction may be applied (according to

Weinberg-Schulz). The significance of a four member sibship is two times greater than that of a two member, that of a six member sibship three times greater, etc. Obviously 3, 5, 7, member sibships have to be multiplied by 3/2,

TABLE 18. BIRTH RANKS OF ANENCEPHALIC PROPOSITI OF THE PRESENT MATERIAL. ABORTIONS ARE NOT INCLUDED IN THIS CALCULATION

TOTAL NUMBER OF SIBS	NUMBER OF ANENCEPHALICS WITH BIRTH RANK 1	2	3	4	5	6	7	8	9	EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER FIRSTBORN	CORRECTED EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER LASTBORN
1	4	—	—	—	—	—	—	—	—	—	—	—	—
2	11	2	—	—	—	—	—	—	—	6.5	11.0	6.5	2.0
3	5	2	5	—	—	—	—	—	—	4.0	7.5	6.0	7.5
4	3	2	1	1	—	—	—	—	—	1.8	6.0	3.6	2.0
5	1	2	—	1	3	—	—	—	—	1.4	2.5	3.5	7.5
6	—	—	—	—	—	1	—	—	—	0.2	—	0.6	3.0
7	—	—	—	—	—	1	2	—	—	0.4	—	1.4	7.0
8	—	—	—	—	—	—	—	—	—	—	—	—	—
9	—	—	—	—	—	—	—	—	—	—	—	—	—
Totals.....	20 = *firstborn*							*lastborn* = 14		14.3	27.0	21.6	29.0

TABLE 19. BIRTH RANKS OF SPONTANEOUS ABORTIONS OF THE PRESENT MATERIAL. ALL PREGNANCIES WITH KNOWN OUTCOME ARE INCLUDED

TOTAL NUMBER OF SIBS	NUMBER OF ABORTIONS WITH BIRTH RANK 1	2	3	4	5	6	7	8	9	EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER FIRSTBORN	CORRECTED EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER LASTBORN
1	—	—	—	—	—	—	—	—	—	—	—	—	—
2	1	—	—	—	—	—	—	—	—	0.5	1.0	0.5	—
3	—	2	—	—	—	—	—	—	—	0.7	—	1.2	—
4	2	2	—	—	—	—	—	—	—	1.0	4.0	2.0	—
5	—	1	1	1	1	—	—	—	—	0.8	—	2.0	2.5
6	—	—	1	1	1	1	—	—	—	0.7	—	2.1	3.0
7	—	1	1	—	—	—	—	—	—	0.3	—	1.1	—
8	—	1	—	—	—	—	1	1	—	0.4	—	1.6	4.0
9	—	—	—	—	—	—	1	1	—	0.2	—	0.9	—
Totals.....	3 = *firstborn*							*lastborn* = 3		4.6	5.0	11.4	9.5

5/2, 7/2, etc. The corrected observed and expected figures in tables 17, 18 and 19 have been calculated according to this principle. When comparing these corrected figures no apparent deviation was found. So our conclusion is that primogeniture or ultimogeniture apparently cannot be claimed as having a connection with anencephaly.

DISCUSSION

Even if we cannot reject fully the idea of anencephaly being caused by some exogeneous factor, no evidence whatsoever has been found in favor of such a conception. On the other hand, the interpretation of the genetical analysis is hampered by the fact that practically nothing is known about the abortion produced by the mothers of anencephalic propositi. On the whole our knowledge about the condition of aborted embryos is very deficient and still remains a gap to be filled by future research.

It is reasonable to assume that the relatively high abortion rate of the mothers in the present material has some connection with anencephaly. The fact that cranio-rachischisis often has been found in early aborted embryos points in this direction. Thus there seems to be a relationship between this condition in man and pseudencephaly in the mouse (cf. Bonnevie, 1936). The conception of a genetical etiology is also supported or is not contradicted by the fact that no systematic deviation is found when the position in the birth rank or the age of the mothers was tested.

As anencephaly occurs with an apparent frequency of about 0.1 per cent, a raised frequency of consanguineous marriages among the parents might be expected, i.e. if caused by a simple recessive lethal with complete manifestation. However, considering that most anencephalic embryos may abort in early pregnancy, and thus are not recognized, the true frequency should be much higher. Furthermore anencephaly and spina bifida might be different manifestation types of the same biological entity, which should increase the apparent frequency to about 0.2 per cent at least. Under such circumstances only a slight increase in the frequency of consanguineous marriages is to be expected, and a very large material would be necessary to make this apparent. This consideration, of course, would imply that cranio-rachischisis was thought of as a genotypical entity.

Actually the very high mutation rate (see p. 77) which would be the consequence of such an assumption forms an objection to this view. However, this estimated high mutation rate might, as indicated on p. 78, represent a sum for two or several different recessive genes. As each one of these genes would have a lower frequency this would work in the opposite direction, i.e. increase the proportion of cases which might be expected to arise from consanguineous matings. It still, however, would be quite small, unless there were a large number of different loci involved.

We think that the theory of anencephaly in man as caused by a lethal genotypical factor (not necessarily meaning one and the same genotypical entity) seems well founded as a working hypothesis to be tested by further research. By that we admit that from a critical point of view the proof of a genetical

etiology has so far not been adduced, although the available data are highly suggestive of such an explanation.

From a practical point of view it is very important to know to what extent abortions and stillbirths in human populations are caused by genotypical factors. For instance, a treatment to retain the embryo in the uterus in threatening abortion when the condition is caused by genotypical factors which have a lethal or semilethal effect is naturally not indicated. There is every reason to believe that such factors are common in human populations just as in natural populations of different animals and plants.

SUMMARY

1. The present study concerns 67 cases of anencephaly belonging to 67 different sibships covering all cases delivered at the Obstetric Departments of Lund and Malmö during 1923–45 and 1917–47 respectively.

2. The incidence of anencephaly in the present material is 0.064 per cent (67 cases out of 104,812 deliveries).

3. The sex distribution was 42 females: 24 males: 1 case of unknown sex.

4. It is estimated that only about 50 per cent of the anencephalics reached a full term development. At least 10 per cent could be classified as late abortions and the rest as premature.

5. Forty-six families (parent-sibships) have been visited and examined by the present authors. No special diseases of the parents and especially of the mothers during pregnancy which could reasonably have a connection with the present malformation have been found.

6. Among the sibs of the anencephalic propositi no further cases of anencephaly were found, but one case of stillbirth with spina bifida was observed.

7. The frequency of abortions among the mothers of anencephalic propositi is significantly increased as compared with a suitable control material of our own.

8. In the present material there is one marriage between first cousins and one between second cousins out of 67 families. Thus a slight increase may be possible, but the material is too small for a proper evaluation.

9. The age of the mothers when the anencephalic children were born corresponds to that expected on the basis of random distribution.

10. Anencephalic children are probably distributed at random throughout the different birth ranks. A special test for primogeniture or ultimogeniture gave a negative result.

11. On the basis of the evidence of this study and in the literature we think that the theory of anencephaly in man as caused by a lethal genotypical factor seems well founded as a working hypothesis. It is then assumed that most anencephalic embryos will abort at an early stage and pass away as undiagnosed

abortions and that full term development (or easily recognized anencephaly) is exceptional.

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The Rare Gene r^y (CdE)

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WHEN the Rh factor was first discovered it was possible to differentiate two new blood types with the aid of anti-rhesus sera. Thus 85 per cent of Caucasians were Rh positive, and the remaining 15 per cent were Rh negative. It became clear through the work of Landsteiner and Wiener (1941, 1942), Levine (1941, 1942), Wiener (1940, 1942), and others that the various human Rh antisera, Rh_0, rh′, and rh″, permitted the differentiation of 8 Rh blood types (Wiener, 1943; Wiener *et al.*, 1947). To account for the hereditary transmission of the eight types, Wiener postulated the existence of a minimum of 6 allelic genes named R^0, R^1, R^2, r', r'', and r, whereas Fisher and Race proposed the existence of three closely linked loci, *C–c*, *D–d*, *E–e*. The assumption that "double action" genes such as R^1 ($R^{0'}$), and R^2 ($R^{0''}$) were transmitted as a single unit led to the speculation that perhaps other "double action" genes, such ar r''', or even "triple action" genes, such as $R^{0'''}$, were thus transmitted. Wiener's early family studies did not reveal such instances. In 1944, while investigating the activity of anti-hr′ serum originally discovered by Levine, Javert, and Katzin and later proved by Wiener, Davidsohn and Potter (1945) to be identical with the *St* serum of Race and Taylor (1943), the latter workers came across some individuals of type Rh_1Rh_2 who were hr′ negative. Family studies revealed the transmission of this gene $R^{0'''}$ as a unit, and thus a seventh allelomorphic gene in the Rh series was established (Race, Taylor, *et al.*, 1943; Race & Taylor, 1944). This gene was incorrectly assumed at first to be r^y, but a more complete family study proved the gene to be R^z (Murray *et al.*, 1945). The designation r^y was reserved for the still unencountered but predicted "double action" gene r'''.

It was not until 1947 that reference to the finding of the rare r^y gene again appeared in the literature, in a report by Stancu, Clark, and Snyder (1947). They commented that because of their rarity the genes r^y and R^z had not been completely established genetically. Their case, however, seems inadequately proven and insufficiently documented for such an important finding. In November, Wiener (1948) reported several families in which the gene R^z was traced and one family in which the rare r^y gene was demonstrated. The first fully presented family study is that of van den Bosch (1948). She clearly traced the transmission of the r^y gene through two generations of a family. Un-

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fortunately, she was unable to complete the entire genetic picture because of the absence of the father. Nevertheless the genetic activity of the r^y gene as a complete unit was clearly demonstrated, and the eighth allelomorph completed the predicted table for the Rh series. In the next month, Wiener and Hyman (1948) reported a family in which three brothers were found to be rh′rh″. The occurrence of this rare blood type in three members of the same family was most plausibly explained by the presence of a single gene, r^y, common to all three. As the wife of one of the men was type rh, his genotype could be proven to by $r^y r$ because their first child was type rh while their second was type rh′rh″.

TABLE 1. RESULTS OF BLOOD GROUP AND RH TESTS

BLOOD OF	GROUP	REACTION WITH ANTISERUM			PHENOTYPE	GENOTYPE
		Rh_0	rh′	rh″		
Patient	A	−	+	+	rh′rh″	$r^y r$
Husband	O	+	−	+	Rh_2	$R^2 r$
Child *No*	A	−	+	+	rh′rh″	$r^y r$
Child *Lu*	A	−	−	−	rh	rr
Child *Ro*	A	−	−	−	rh	rr

TABLE 2. RESULTS OF BLOOD GROUP AND RH TESTS

BLOOD OF	GROUP	REACTION WITH ANTISERUM			PHENOTYPE	GENOTYPE
		Rh_0	rh′	rh″		
Father of patient	A	+	−	+	Rh_2	$R^2 r$
Mother of patient	A	−	+	+	rh′rh″	$r^y r$, $r^y r'$, $r^y r''$ or $r^y r^y$
Sister of patient	A	+	+	+	Rh_1Rh_2	$R^2 r^y$

While performing routine antenatal studies we have encountered a family in which the hereditary transmission of the extremely rare r^y gene, which has a frequency of about 0.01 per cent, could be completely traced through three generations. Since there are no such cases on record, it will be reported in detail.

CASE REPORT

Mrs. O was referred for study with her husband and three children because she was found to be of type rh′rh″ (Rh_0 negative). She was gravida 4, para 3, and her expected date of confinement was October, 1949. Her children were living and well, and there was no history of neonatal anemia or jaundice. The

results of the blood grouping of the immediate family (table 1) indicated the presence of the rare r^y gene, and therefore the entire available family was studied (table 2).

Dr. Alexander S. Wiener, in corroborating the above findings, very kindly

TABLE 3. RESULTS OF COMPLETE BLOOD GROUPING, RH AND HR TESTS

BLOOD OF	REACTIONS WITH ANTISERA SPECIFIC FOR ANTIGENS:											PHENOTYPE AND (RH-HR GENOTYPE)	
	A	B	A_1*	M*	N*	Rh_0	rh′	rh″*	rh‴	hr′	hr^y		
Father	+	−	+	+	+	+	−	−	+	+	+	A_1 MN Rh_0rh	(R^2r)
Mother	+	−	−	+	+	−	+	−	+	+	+	A_2 MN rh′rh″	(r^yr)
Sister	+	−	+	−	+	+	+	−	+	+	−	A_1 N Rh_1Rh_2	(R^2r^y)
Patient	+	−	+	−	+	−	+	−	+	+	+	A_1 N rh′rh″	(r^yr)
Husband	−	−	0	+	+	+	−	−	+	+	+	O MN Rh_0rh	(R^2r)
1st Child (*No*)	+	−	−	+	+	−	+	−	+	+	+	A_2 MN rh′rh″	(r^yr)
2nd Child (*Lu*)	+	−	−	−	+	−	−	−	−	+	+	A_2 N rh	(rr)
3rd Child (*Ro*)	+	−	+	+	+	−	−	−	−	+	+	A_1 MN rh	(rr)

* Tests performed by Dr. Alexander S. Wiener.

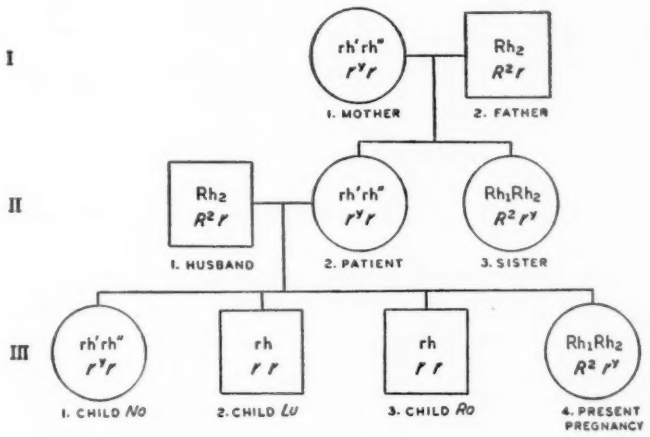

FIG. 1

completed the study by determining the reactions with hr″ antiserum as well as anti-M and anti-N sera (table 3). We wish to emphasize at this point that the genotypes of all members of this family except for the patient's mother, could be fully determined by the use of the three Rh antisera, anti-Rh_0, anti-rh′, and anti-rh″, and the distribution of the Rh types in the family. In the

instance of the above exception, anti-hr′ and anti-hr″ sera indicated the patient's mother to be heterozygous and of genotype $r^y r$. In all other members of this family the use of anti-hr′ and anti-hr″ sera served only to confirm our previous deductions.

DISCUSSION

Persons of type rh′rh″, such as our patient Mrs. O, usually have the genotype $r'r''$ and thus cannot have type rh children. As two of the patient's children belong to type rh, Mrs. O is to be reckoned a bearer of the gene r and therefore is of the rare genotype $r^y r$. Mr. O, the husband, is of type Rh_2, and since he is the parent of two type rh children, he is of genotype $R^2 r$. It is thus clear that the first child (*No*), who belongs to type rh′rh″, must be of genotype $r^y r$. Our patient must have inherited her r^y gene from her mother, who is of type rh′rh″. Her father, who belongs to type Rh_2, must be heterozygous in order to have transmitted an r gene to his daughter. Our patient's sister, who belongs to type Rh_1Rh_2 must have inherited an R^2 gene from her father and an r^y gene from her mother.[1] This established the genotypes of all members of the pedigree except for our patient's mother in whom only one gene can be identified with certainty, namely the r^y gene, since both of her offspring carried this gene. She could be either $r^y r^y$, (frequency 0.000001 %), $r^y r''$ (frequency 0.0001 %), $r^y r'$ (frequency 0.0003 %), or $r^y r$ (frequency 0.01 %) (Wiener, 1949*a*). That her actual genotype is $r^y r$ is proven by her positive reactions with hr′ and hr″ antisera.

The controversy concerning the multiple allele theory versus the three-locus theory for the genetic transmission of the Rh types has been frequently discussed during the past several years. Intimately bound to this problem is the related difficulty in the respective terminologies advocated by Wiener (Wiener & Sonn, 1945, Wiener, 1949*b*) on the one hand and by Fisher and Race (1946) on the other. It has been said that if the "double and triple action" genes such as R^1, R^2, r^y, and R^z were known to be invariably inherited as units and never split into component parts, then the multiple allele theory would be confirmed, whereas evidence that they are even rarely inherited as parts would substantiate the three locus theory (Potter, 1947). The above case traces the transmission of the rare gene r^y as a unit through four persons over three generations, with no evidence of dissociation. Likewise the clarity of description of both phenotypes and genotypes is demonstrated for the abbreviated Rh-Hr nomenclature due to Wiener.

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[1] Based on this reasoning, it was predicted that this individual's blood should be hr″ negative, as was indeed subsequently confirmed.

SUMMARY

A case is presented which demonstrates the existence and hereditary transmission of the rare gene r^y in four persons through three generations.

The authors wish to express their sincere appreciation to Dr. Alexander S. Wiener for corroborative tests performed by him.

Addendum: Since preparation of this paper, the "present pregnancy" terminated in the delivery of a normal female child of blood group A. Her blood cells gave positive reactions with anti-sera Rh_0, rh′, rh″, hr′ and negative reaction with hr″ (fig. 1). This corresponds to phenotype Rh_2Rh_2; however, from knowledge of the genotypes in the family, this child's genotype is evidently R^2r^y.

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BOOK REVIEWS

Mongolism and Cretinism

By CLEMENS E. BENDA. New York: Grune & Stratton, 1949. Pp. 316, with 104 illustrations. $7.00.

THIS is a new edition of a book first published in 1946 under the same title. According to the author, "the present edition is revised where further research offers new data," and furthermore, Chapter 10, containing "the basic data as to the etiology of mongolism". . . "has been thoroughly revised."

The monograph offers a great deal of material of interest to the clinician and pathologist. A considerable amount of work lies behind the author's observations on the pathology and pathogenesis of the disease. Much of his data on such features as brain and spinal cord pathology and the development of endocrine glands in mongolism is quite new and original. Dr. Benda is to be congratulated on the excellent material he presents in this portion of his study. His main conclusion seems to be that mongolism, or, more correctly, congenital acromicria, is clinically and pathologically characterized by a specific deficiency of physical and mental growth and endocrine metabolism. The main structure impaired appears to be the pituitary gland, which shows evidence of probable insufficiency at an early embryonic stage. To be sure, it is not possible to prove conclusively that the primary defect is located in the hypophysis, the cerebral cortex, the hypothalamus, or some other localized area of the central nervous system. However, the author gives a number of good arguments for considering the hypophysis to be the organ which is primarily involved in mongolism.

It is perhaps appropriate to limit the review of the first nine chapters to the above remarks, since the readers of this *Journal* are probably more interested in those sections dealing with the etiology of this disease. The author's knowledge and experience with the clinical pathological features of this defect are undoubtedly excellent. However, as is often the case in the field of medicine, the interpretations are open to argument.

Dr. Benda's contribution to the etiology of congenital acromicria is a definite disappointment to the reviewer. I will begin with some general remarks, and follow with more detailed examples. My criticism is especially directed towards the author's remarks in chapters 10 through 12. In a scientific study, the basic data should be presented in such a fashion that the reader can easily verify the conclusions by rechecking the data. In the present book the presentation of material is confusing, and information relating to important data is often vague or completely lacking. Dr. Benda seems convinced that genetic factors are of no etiological significance in congenital acromicria. In attempting to prove this to the reader, however, he unknowingly commits serious mistakes, due apparently to unfamiliarity with the exacting methods of genetic study. The proof or disproof of hereditary factors in disease requires thorough *clinical* and *genetical* study, with precise and correctly collected data. Medical genetics has now become as much a specialty as have other branches of medicine, and the clinician who gallops into the field will be in somewhat the same position as the psychiatrist who rushes into the field of major surgery.

A complete and detailed criticism would take too much space and time, so only a few of the more important points will be considered. Dr. Benda's material consists of 500 families (p. 248). A little later on the same page he refers to 255 cases, evidently included in the above families, and on page 267 he mentions 75 cases. The author does not state how these cases or

families were selected, nor how they were examined. On page 252 he says "In spite of the fact that I had access to 500 case histories, only 5 families were found with more than one mongoloid child, besides the cases of concordant mongoloid twins mentioned above. In one family, 2 out of 13 living children were mongoloids; in one family all 3 children were mongoloids; in one, 2 of 7; and in two, 2 of 3." That makes 6 secondary cases. Referring back to see what is meant by "twins mentioned above," one reads on page 250; "more than 80 twins with mongolism have been reported in the literature." Dr. Benda neglects to say among how many sibs these 6 secondary cases were found, and on page 250 he says "although reliable data concerning the incidence of familial mongolism are scanty, one may reasonably assume that no more, and probably less, than 1 per cent of affected sibships show more than 1 mongoloid." A conclusion concerning the incidence of congenital acromicria among the sibs can be based only on personal examination of families, and not on studies of case histories, questionnaires or data collected by unskilled field workers. Since Dr. Benda's data do not appear adequate for genetic analysis, no conclusion can be drawn. His statement on page 248 "My own material of more than 500 families accumulates evidence that hereditary factors are of no importance" is thus not supported by any of his own facts as they are presented in this monograph.

On page 250, twin data taken from the literature are brought into the discussion. This is a dangerous step, inasmuch as only unselected twin series can be used in drawing scientific conclusions, a tenet well known to all who are familiar with the basic principles of medical genetics. And, moveover, if the available twin data can be considered to suggest anything, it is that hereditary factors have some importance (see table):

	Concordant	*Discordant*
Monozygotic	7	–
Dizygotic, same sex	4	21

It is quite apparent that Dr. Benda is unfamiliar with the two basic methods of medical genetics, namely twin research and family research, thereby making it impossible for him to draw valid conclusions regarding the significance of possible genetic etiological factors.

On page 264 appears the statement: "2. The frequency of abortions is one of the most striking features in case histories of mongolism." Now, let us see how this conclusion is reached by the author. He states: "1. A percentage of 9.8 pregnancies terminate in spontaneous abortion. 2. Among 255 mothers of patients with mongolism, 80 or 31.2 per cent had one or more abortions." Dr. Benda then concludes, "this indicates a three times higher rate of spontaneous abortions than in the general population." The correct procedure for evaluating this point would have been as follows. The 225 mothers in his material had 924 (table 37) live births (propositi subtracted) plus 126 abortions, or a total of 1050 pregnancies. Thus, 126, or 12%, of the pregnancies ended in abortion. The only conclusion that can be drawn from this is that the rate of abortion in Dr. Benda's material is not significantly raised.

Dr. Benda states (page 267) that "The maternal condition at the time of pregnancy is the decisive factor for the fetal growth disorder," evidently disregarding his own review of twin cases, in which the greater number of dizygotic discordant twin pairs argues strongly against such a viewpoint. He cites 67 case histories to support his conclusion. These include such indefinite disorders as "felt different, deadly sick," "put on 20 pounds during pregnancy, easily upset", "renal hypertension," "anxious, easily upset", etc., which supposedly occurred during the pregnancy which terminated in the birth of a mongoloid child. To anyone acquainted with obstetrics, these conditions, with the possible exception of a bleeding tendency in a few cases, represent anamnestic findings of no special significance. Moreover, it

is well known that women who have borne defective children always try to find the cause for it, and will magnify minimal symptoms. Dr. Benda says (page 274): "No one who glances through the series of case histories above can escape the conclusion that the cause of mongolism is to be found in the condition of the mother at the beginning of pregnancy." The reviewer is unable to find any facts in the book which will support this conclusion. Perhaps the difficulty is that there was too much "glancing" through case histories throughout the course of Dr. Benda's research work.

In my opinion, no conclusive evidence has so far been produced for or against heredity in mongolism, and the present monograph does not add anything new to this discussion. However, there is much in favor of an hypothesis that hereditary factors are of importance. The following, so far reported by different authors in this field, may be mentioned: the slight increased incidence of mongolism among the sibs; the collected data about twins (given their proper evaluation); and the probably increased abortion frequency. Perhaps at least some of these abortions may be genetically mongoloid, which would then increase the familial incidence. It might be worthwhile to test the following speculation which would appear to fit most of the present data concerning congenital acromicria. Suppose that the condition is due to a single recessive gene which in most homozygotes is lethal (effect is to raise the abortion rate) but only in very few cases permits the embryo to develop to full term (congenital acromicria). This would mean a rather high rate of mutation and such a high frequency of the gene in the population that no appreciable increase of consanguineous marriages could be expected. The fact that most mongoloids occur at later birth rank and are borne by elderly women may be due to a different response of the mother to the pathologic embryo at a different age. By that I fully realize the importance of a maternal factor (yet unknown), but the present data point also to a primary factor operating in the embryo.

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The Biology of Mental Defect

By LIONEL S. PENROSE (Galton Laboratory, Gower Street, London W.C.1, Eng.). New York: Grune & Stratton, 1949. Pp. xiv + 285, with 7 plates and 11 text figures. $4.75.

THE author of this book, the distinguished Galton Professor of Eugenics at University College in London, has made an outstanding contribution, not only to the field of mental deficiency, but also to that of psychology and medical genetics. That he is able to write authoritatively of a subject whose roots lie deep, not only in clinical medicine, but also in sociology, psychology and genetics, is a tribute to his unusual personal training in each of these fields. The inclusion in this volume of some of the findings from his monumental research into the causes of mental deficiency, carried out in England between 1931 and 1937 (known as the Colchester Survey), lends both singular stature and freshness to the book.

Following a brief historical review, Dr. Penrose discusses the incidence, definition, measurement, and the basic principles of classification of mental defect. He points out that such traditional dichotomies as 'congenital' and 'acquired', 'endogenous' and 'exogenous', are less useful today since nature-nurture relationships are too intimately inter-related and inter-dependent.

The problems of causation, in which the importance of the gene is emphasized, are thoroughly examined. Since cases of mental defect are usually present at birth or soon after, at least part of the causation must lie in the biochemical action of the gene. Dr. Penrose discusses methods of analysis in human genetics which may be utilized in discovering the modes of inheritance of many cases of mental defect. He emphasizes that each case is dependent upon the combined influences of heredity and environment and that it is misleading to ask which is the more important influence. He also examines methods of distinguishing between nature and nurture. Of significance are the discussions of hereditary diseases which may be associated with cases of mental defect: (1) rare *dominant* defects, i.e., Huntington's chorea, epiloia, dystrophia myotonica, neurofibromatosis, acrocephaly, and arachnodactyly; (2) rare *recessive* diseases, i.e., phenylketonuria, microcephaly, cerebral diplegia, choreoathetosis, Friedreich's ataxia, Tay-Sachs' disease, juvenile amaurotic idiocy, gargoylism, and retinitis pigmentosa; (3) rare *sex-linked* diseases, i.e., anhidrotic ectodermal dysplasia, and microphthalmia. The causation of such fetal malformations as anencephaly, spina bifida, hydrocephaly, and mongolism is regarded as one of the most baffling medical problems. His conclusions as regards the cause of mongolism are: "...the mode of action of the hereditary background is obscure and is much less important, from the point of view of preventive treatment, than the environmental factors dependent upon maternal conditions." He finds that the age of the mother at the birth of a mongol child averages about 37 years, compared with a mean age of 29 years for all births. Among other defects of obscure origin that are discussed are fetal infections and prenatal cerebral injury. Earlier American findings that the Rh factor may play a very important role in undifferentiated cases of mental defect, have not been borne out, according to Dr. Penrose.

He analyzes the available evidence concerning the intelligence of parents and siblings of mental defectives and correlations for intelligence between relatives. In regard to reported differentials in the birth rate statistics and the gloomy predictions of some people of a decline in world intelligence, Dr. Penrose holds to a more conservative and hopeful position: "So far, no direct evidence of declining intelligence in any modern community has been presented, and there are...reasons for doubting the full implications of the arguments by which its prediction is supported." He also suggests the need for a tolerant attitude toward the defective population. He writes: "High-grade and borderline mental defect are phenomena which have come into prominence only since human life has become urbanized and industrialized. Civilized communities must learn to tolerate, to absorb and to employ the scholastically retarded and to pay more attention to their welfare." And elsewhere: "The ability of a community to make satisfactory provision for its defectives is an index of its own health and progressive development; the desire for their euthanasia is a sign of involution and decay of human standards." The author is not in agreement with recent advocates of sterilization as a method of prevention. He writes: "From the biological point of view, the effects of limited use of voluntary sterilization are likely to be negligible, though considerable medical and social advantages might be obtained by its use in carefully picked individual cases....It is difficult to justify compulsory sterilization of defectives on genetical grounds."

The section on eugenic prognosis should be eagerly received by those who must frequently advise the relatives of mental defectives as to the chances of any future children of theirs suffering from the same disease. For example, where both parents are of normal intelligence and have had one child of idiot or imbecile grade (with unspecified diagnosis), the chances that other siblings will be of similar low grade, is almost tenfold as compared with the population incidence. As for intelligence as a whole, the evidence seems to be that the mean intelligence of children approximates the average level between the parents.

There is an excellent bibliography which contains references to works of historical or basic interest and also some which are typical of recent research. It will probably be a pleasant surprise to many readers to find numerous references to human and medical genetics in a book on mental deficiency. The book contains an Index, seven Plates of photographs of mental defectives, and ten Appendices of statistical tables.

Both lay and professional readers will find this volume unique and indispensable. Dr. Penrose omits a detailed discussion of clinical types and the more specialized medical aspects of the problem. It is hoped that he will, in the near future, give us the definitive treatment of the subject of mental defect that would include these more specialized aspects. Professor J. B. S. Haldane once said, referring to an earlier book of Penrose: "This work has lifted the whole study to a new and higher level." It is to be felt that this is just as applicable to the present book.

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Mathematical Methods for Population Genetics

By GUNNAR DAHLBERG (State Institute of Human Genetics, Uppsala, Sweden). Basle, Switzerland, and New York: S. Karger, Ltd., 1947. Pp. viii + 182, with 32 text figures. sFr 25.—

ONE current development of particular significance to the study of heredity in man is a growing interest in population genetics. The mathematical methods necessary for an evaluation of the interplay of mutation, selection, isolation, migration, and gene frequency drift in man, insofar as those methods have been developed at the present time, have appeared in widely scattered journals during the past several decades. Many of those interested in such problems have felt the need of a treatise which would assemble and evaluate these mathematical techniques. This book by Dr. Dahlberg, a German edition of which was published in 1943, represents an attempt to do just that.

The opening chapters are devoted to a brief consideration of the different forms of inheritance, and the proportions in which, assuming panmixia, the constituent genotypes occurring in the various forms of inheritance are represented as gene frequencies vary from 0 to 1. There follow chapters on the effects of mutation and selection on gene frequencies, and a consideration of the interplay of these two factors. Next, the influence of consanguineous marriage and assortative matings on the composition of populations is taken up, followed by a consideration of the importance of isolates in attempts to evaluate the overall genetic composition of a population. The final chapters are devoted to developing the interaction of such factors as mutation, selection, and isolates; isolates and consanguineous marriage; and isolates, assortative mating, and selection. The concluding chapter contains a discussion of some of the concrete problems in human heredity to which the mathematical methods of the preceding chapters are applicable. The sequence of topics appears logical, and the subject matter well chosen. Although some will doubtless differ with the author concerning the relative emphasis accorded various topics, this is after all largely a matter of subjective opinion at the present time. Thus, the stress placed on isolates, and the tendency to minimize the significance of mutation, will not find ready acceptance in all quarters. It seems strange that there is practically nothing on the estimation of linkage, a topic of first

order magnitude in any consideration of the retention of group characteristics when an isolate is broken up. This omission is underlined by such a statement as is found on page 67: "In panmixia we should expect characters to occur together at random in the same person. If there is linkage, they should occur together more often."

The author has made a studied effort to render the book "comprehensible to persons with no mathematical training," and in this attempt he must be adjudged quite successful. But while much can be said for this attempt, insofar as it serves to introduce the field to many who might be frightened off by a more sophisticated approach, it seriously limits the thoroughness with which any given topic can be explored. The inevitable result is that the investigator going to this book with a specific problem will frequently find that it falls short of his needs, and he must refer to the original sources; unfortunately, these are not always clearly indicated. The reviewer detected only one mathematical error in the derivation of the 94 major equations found in the book, this on page 97, where it is stated that $r_t = \sqrt{r^2 + \sigma_i^2}$, r_t being the frequency of a recessive gene in the population, r^2 the frequency of individuals exhibiting the trait due to homozygosity for the gene in question, and σ_i^2 being an expression for the excess of recessive homozygotes over expectation on the basis of panmixia which is produced by isolate effects. The correct formula would either appear to be $r_t = \sqrt{r^2 - \sigma_i^2}$, or else the reviewer has been led to misinterpret the definitions of r and r_t.

In places the book suffers from a lack of clarity which is perhaps due in part to the fact that the author is attempting to over-simplify and is not writing in his native language. Thus, in a brief chapter on "Selection and Mutations," the author writes (p. 50):

"If, now, mutations appear in a population, and if the character-bearers arising thence are subjected to selection, the process must approach a state of balance, when the number of mutations correspond to the number of character-bearers disappearing as a result of selection. For example, in monohybrid recessivity if the gene has the frequency r and the mutations the frequency μ, a state of balance should be set up when $r^2 = 2\mu$."

This statement, which is not further qualified in that chapter, is true only if μ is interpreted as the mutation rate per (diploid) individual per generation rather than, as is the more usual custom, the mutation rate per gamete (or per gene per generation), and only if the coefficient of selection against the homozygote (r^2) is 1, or the fertility of the homozygote is 0, and if consanguineous marriage in the population approximates that demanded by panmixia.

Again, on page 91, we find the statement: "Let us assume that b is the average number of children who become adult and marry in each sibling-group, and that n is the number of individuals of this kind in the entire population. If we now select an individual at random from the population, he will have on an average $b(b-1)$ cousins to whom he can get married. The total number of individuals to whom he can get married is $\frac{n}{2}$. The probability for a cousin marriage c is thus:

$$c = \frac{2b(b-1)}{n} \quad \text{and} \quad n = \frac{2b(b-1)}{c}.$$

"When drawing up this formula it was not necessary to take into account differences of sex since an individual cannot marry another of the same sex."

This last sentence will confuse the average reader, since inasmuch as the number of *first* cousins under these assumptions is $2b(b-1)$, a correction for sex has certainly been unobtrusively introduced, while division of n by 2 is again a correction for sex.

As the book stands, there is a paucity of illustrative material, only partially offset by the discussion in the final chapter. This may reflect a deliberate choice on the part of an author

attempting to keep his book brief. Furthermore, it must be admitted that so little work has been done on the subject that for many topics it would be difficult to find pertinent illustrative material. It is noteworthy, however, that the discussion of the role of mutation in population problems, to take only one example, is carried out with no reference to the mathematical problems actually encountered in the four attempts to estimate mutation rates which had appeared when this book presumably went to press in 1946.

The author has made a valuable contribution in organizing a difficult area of interest. The 182 pages illuminate a wide variety of topics of importance to population genetics. Perhaps it is too soon to expect the definitive treatise which the title of this book would lead one to anticipate.

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The Theory of Inbreeding

By RONALD A. FISHER (Department of Genetics, Cambridge University, Eng.) Edinburgh, London: Oliver & Boyd, Ltd., 1949. Pp. viii + 120, with 9 text figures.

MATRIX algebra is used for estimating the proportions of various kinds of matings under a few rather intense inbreeding systems. The frequencies of the kinds of matings in one generation are expressed in terms of their frequencies in the preceding one, thus forming the generation matrix. Jennings used this approach in 1916 (*Genetics*, 1: 53–89) in one of the first major attempts to deduce the Mendelian consequences of breeding systems, but did not carry it so far. Professor Fisher does not mention this nor Wright's monumental work on mating systems in 1921 (*Genetics*, 6: 111–178) which was later extended (*Genetics*, 16: 97–159) to include the inbreeding consequent on finite size in natural populations, and still later to include sex-linkage (*Proc. Nat. Acad. Sc.* 19: 411–420), polyploidy (*Proc. Nat. Acad. Sc.* 24: 372–377), the effects of self-sterility genes (*Genetics*, 24: 538–552), isolation merely by distance (*Genetics*, 31: 39–59), and many other details in various papers. Obviously no review of literature was intended in the present book, since only eight references are mentioned, five of which are Fisher's own writings. The other three are one each by Darwin, by East and Jones, and by Ford.

The theory of inbreeding presented is all in the first six pages, except for the mathematical formulation. It is simply that the primary effect of inbreeding is to destroy heterozygosis and that, as between any two alleles at a given locus, the dominant is almost always the more favorable. Ascribing the unfavorableness of the results wholly to dominance neglects some other situations in which inbreeding would cause a decline in average phenotypic merit, even though the genes might not show any dominance in their primary effects. One example of such a situation is the probably frequent one in which an intermediate is preferred to either extreme. In that case, inbreeding will automatically cause a decline in average phenotypic merit, merely because it increases the zygotic variance on the primary scale. Another example is the case of threshold effects, where again the genes need not have any dominance on their primary scale and yet the effect of inbreeding in increasing the variation would throw a larger fraction of the population below the threshold at which harmful effects begin to appear. Dominance may well be the major factor in making pheno-

typic merit decrease as heterozygosis decreases, but it can hardly be as nearly the sole factor as Fisher implies when he says (page 3) of dominance: "Without it we could give no explanation of the effects of inbreeding, for the only effect which inbreeding can have, in accordance with the law of segregation, is to increase the frequency of the two kinds of homozygote equally at the expense of the frequency of the heterozygote. In the absence of dominance this can have no effect on the average, but can only increase the variability among the offspring of a self-fertilization, or a union of close relatives."

Professor Fisher takes occasion to reaffirm his belief that dominance generally arose by natural selection of genes which modify the phenotype of the initially intermediate heterozygote. He even adds (page 4) that this "appears now to be found generally acceptable." He still misses the main reason that many biologists think this can be true only in extremely exceptional cases, since he insists that "its only questionable premise" was that "the reaction of the heterozygote is readily modified by the selection of modifying factors." Instead almost everyone has agreed, even from early in the work of the Morgan group on *Drosophila*, that this could sometimes happen when circumstances caused selection for the modifiers to become a first-order force as, for example, in a stock where selection keeps the heterozygote extremely abundant, or as the expression of the homozygous recessive may be modified in a stock kept for a long time homozygous for that gene but segregating for many other genes. The major reason for doubting that dominance has generally come about by selection of modifiers, as Fisher proposed two decades ago, is still the extreme improbability that sufficiently many modifying genes would often be floating around heterozygous in the population and *doing so little else on their own account* that their equilibrium frequencies would be shifted appreciably by making such an extremely faint change in their selection coefficients. The change would be faint because selection for a gene's modifying effects would operate only in the tiny fraction of the population heterozygous for the newly arisen primary gene whose heterozygous manifestation is to be modified. On the other hand selection for or against the modifier on account of any direct effects of its own would operate on it in all the population. With selection for its modifying effects being thus a second-order force, but selection for its own primary effects being a first-order force, the balance of these forces would rarely be so delicate that introducing the second-order one would shift appreciably the equilibrium frequency of the modifying gene. Admittedly this reasoning is colored by one's ideas of how many different effects a gene usually has, the frequency of mutations, whether the equilibrium frequencies of modifying genes are generally near zero or near 1.0 or in the middle of the range, how many heterozygous loci a population can support, etc. This is not the place to review that controversy in detail. Whether dominance originated in one way or another is not pertinent to the general argument of the book. Yet clarity does require calling attention to Professor Fisher's misinterpretation of what premise in his original theory is the main questionable one. Unfortunately the nature of the problem seems to defy direct experimental attack, since selecting for the modified expression of the primary gene in a population which is deliberately kept largely heterozygous raises the modifying effects of the modifying genes automatically to first-order effects instead of letting them remain the second-order effects they would be in a natural population where the newly arisen gene is extremely rare.

Chapter 2 on inbreeding a line while still maintaining segregation for one or more pairs of genes with manifest effects touches on several topics of practical import to the laboratory geneticist. Among them are the number of young needed if the investigator is to be reasonably sure of getting at least one eligible mating, the extra requirements when more than one pair of genes are to be kept segregating, and the effects of linkage on these requirements.

The chapter concludes with a brief and illuminating discussion of the kinds of genetic problems for which segregating inbred lines are especially useful.

Chapter 3 explains the mathematical method of analysis, using full sib inbreeding as the example. The generation matrix is set up in a form general enough to include multiple allelism in diploids. Polyploidy is treated later on pages 78 to 95. Primary emphasis is on the proportions of the various kinds of matings, rather than on the proportions of the various kinds of zygotes. The matrix algebra is intricate. Most readers will find the formulas complex and tedious to follow. The main goal of the formulas is the derivation and use of *lambda* which is defined (page 28) as the frequency of a kind of mating in one generation divided by its frequency in the preceding generation. Under a regular system of inbreeding, λ reaches some constant value within a few generations after the inbreeding begins. Then the relative frequency of the non-homogeneous matings remains constant, although they all decline in absolute frequency at the rate, $u_{n+1} = \lambda u_n$. Then this λ becomes just another expression for F, the coefficient of inbreeding which Wright proposed nearly three decades ago. From the time the proportions of the different kinds of matings reach equilibrium under the given inbreeding system, F and λ are related as follows: $1 - F = \lambda^n$, or $\lambda = \frac{1 - F}{1 - F'}$. This renders pointless the derogatory comment on page 43 concerning inbreeding coefficients: "It is this which renders attempts to set up coefficients of inbreeding unsatisfactory." Moreover, Wright's F is much more easily calculated than Fisher's λ, especially when there is some irregularity in the inbreeding system or when the kinds of matings have not yet reached equilibrium proportions.

Most of the conclusions reached in this chapter were stated in simpler form by Wright long ago. For example, the equilibrium frequency of the three segregating mating types which Fisher gives on page 40 can be seen on page 112 of *Genetics* in 1931 as Wright states them, except that Fisher has combined Wright's types $Aa \times aa$ and $AA \times Aa$. On the same page is Wright's statement that the frequencies of the segregating matings are falling 19.1 percent per generation, which is simply the complement of Fisher's $\lambda = .809017$ under sib-mating, as given on page 43. Other than the mathematical method of analysis, the only material topic in Chapter 3 which was not covered by the much earlier work of Wright is in pages 49 to 61 which treat of the fate of genes in the tracts of chromosomes adjacent to the loci of dominant genes which were introduced into the stock and then were kept segregating for them while full-sibbing the stock. The average delay in approach to homozygosis, for genes on the same chromosome with those kept segregating, is concluded to be 1¾ generations (page 61).

The 38 pages of Chapter 4 are devoted to other systems of inbreeding, mostly regular. These systems and many more had already been elucidated by Wright in 1921, and in more detail in 1937 when he discussed inbreeding and sex-linked genes and also the results of inbreeding in polyploids, but it seems clear that Fisher had not seen these articles since he states (page 62): "I do not know that any of these systems have been previously elucidated; certainly, the practical results of examining them appear to be entirely unknown, and writers often discuss inbreeding as though the system of sib-mating were the only one available." The original parts of this chapter, other than the mathematical method of approach, concern what happens when the concurrent selection and the choice of matings are such that one or more chosen genes are kept segregating.

Appendix A is nine pages on ways of minimizing the delay which variations in the sex ratio must often cause in increasing the inbreeding in species with single births. For example, a system of mating the first offspring of unlike sex to the younger parent will give the same

rate of inbreeding per generation as a system of full-sibbing but on the average will save the time of one birth interval per generation in species with single births. These topics are practically important but they are solved more easily, including the irregularities sure to arise in actual practice, by Wright's coefficient.

The six pages of Appendix B treat of the extent to which selfsterility mechanisms retard the approach to homozygosity by preventing certain fractions of the parent-offspring or full-sib matings which might otherwise occur.

Appendix C is five pages on the use of inbreeding in plant and animal improvement and deals largely with hybrid corn. The effect of eliminating the undesirable recessive genes is not nearly enough to account for the success of hybrid corn. He considers this from the balance between selection and mutation rates and concludes that: "Perhaps no more than a 1 per cent improvement could be looked for from this cause." This is going a bit further than Crow who by a similar argument, had already concluded (*Genetics*, 33: 477–487) that 5% was about the outside limit of what could be achieved in this way. Fisher attributes the success of the hybrid corn program to selection between the lines for their known performance in crosses but he does not go into detail concerning what forms of gene interaction are likely to explain the resulting heterosis, except to say that overdominance would explain the observed heterosis in first crosses but not in later crosses (such as three-way crosses or the widely used double crosses) "... unless a multiplicity of alleles, all deleterious when homozygous, were assumed." It seems to the reviewer that a multiplicity of *loci*, all showing overdominance, would explain heterosis in later crosses as well. The actual first crosses which we yet know probably have not reached the theoretical maximum heterosis which will occur when the two inbred lines crossed are so perfectly matched that they differ in every one of the loci where overdominance occurs. This seems the simplest explanation for the generally high success in predicting the yield of double-crosses of corn. The double cross of four inbred lines can be made in three different ways, according to which two of the six possible single crosses are crossed with each other. The actual yield of the double cross is generally very close to the average yield of the four first-crosses not used.

In summary, the major accomplishment of this book is to confirm by methods of matrix algebra what was long ago shown by Wright with path coefficients and has already become widely used. This will be welcomed by those readers who are allergic to correlation methods or who for other reasons have been uncertain about the validity of Wright's methods and conclusions. The many who long ago accepted Wright's findings and have been using them for varied purposes will find this book useful only for a few details about practical applications and for its attention to what happens when a population is being inbred but at the same time is kept segregating for one or more pairs of chosen genes. The geneticists who will find it most useful are those who are preparing special stocks of prolific animals for laboratory genetic research purposes. It appears not to have much application to research in human genetics since the intense inbreeding systems treated do not occur in man, or at least do not continue long enough for the frequencies of the various kinds of matings to settle into equilibrium.

It is a distinct loss to the readers that the author did not include enough of a historical review of the more important earlier and widely used works in the field that it would be easy to see where his findings confirm or disagree with those. The reviewer noted no disagreements which seem important, but did see a number of slightly but usefully different ways of expressing ideas already familiar in other verbal forms.

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THIS section, prepared by the Editor, continues the current list of research articles and books of interest to students of human genetics. For information concerning the arrangement of titles, abbreviations of medical serials, and authors' addresses, see Part I of the 1949 list (*Am. J. Human Genet.* 1: 105–112).

Numbers placed in square brackets following citations in the present list ([1], [2]) refer to earlier parts of the current 1949 list, where the author's address is provided.

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The brief but well-planned and plainly suspicious histories of the American Society of Human Genetics and the American Journal of Human Genetics are already a matter of record. Both the society and the journal are now in their second year of life, and all the notable aspects of their deliberative conception, functional purpose and earliest development have been duly recorded by the first president of our organization, Professor H. J. Muller.

What is still to be acknowledged is the generous financial aid received from the Coolidge Foundation in the launching of the Journal. Everyone knows that giving birth to a new scientific magazine is almost as difficult as, and probably even a little more expensive than, having a real baby. That the birth and babyhood of the Journal have been smooth we owe to a large extent to the liberal grant provided by the Coolidge Foundation. The appreciation of our membership is due not only to the trustees and officers of the Foundation, but also to those who helped in negotiating the grant. Especially valuable parts in these negotiations were played by Dr. Nolan D. C. Lewis, Columbia professor of psychiatry and editor of another noted journal sponsored by the Foundation, the *Journal of Nervous and Mental Diseases*, and by Dr. Franz J. Kallmann of the New York State Psychiatric Institute.

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